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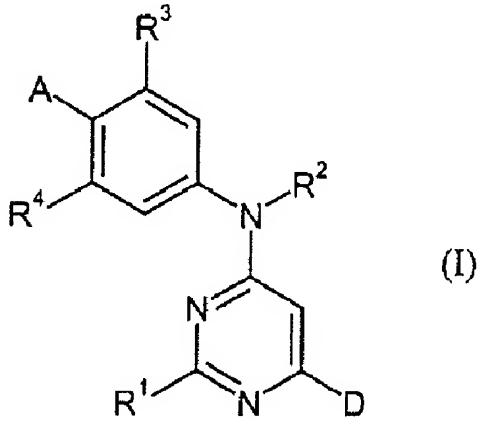
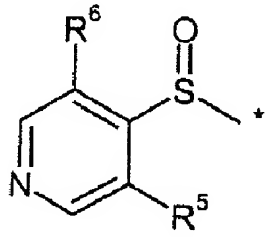
(72) Inventeurs/Inventors:
FEURER, ACHIM, DE;
BENNABI, SAMIR, DE;
HECKROTH, HEIKE, DE;
ERGUEDEN, JENS, DE;

(54) Titre : PHENYLAMINOPYRIMIDINES ET LEUR UTILISATION EN TANT QU'INHIBITEURS DE LA RHO-KINASE
(54) Title: PHENYLAMINOPYRIMIDINES AND THEIR USE AS RHO-KINASE INHIBITORS



(I)



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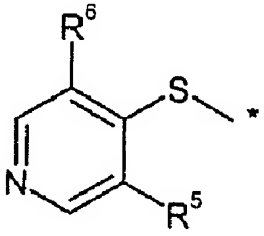

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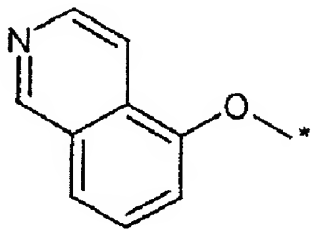

(IV)

(57) Abrégé/Abstract:
The invention relates to phenylaminopyrimidines and processes for their preparation, and to their use for preparing pharmaceuticals for the treatment and/or prophylaxis of diseases, in particular cardiovascular diseases. In a specific embodiment,

CA 2489452 C 2011/08/23
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(72) Inventeurs(suite)/Inventors(continued): SCHENKE, THOMAS, DE; BAUSER, MARKUS, DE; KAST, RAIMUND, DE; STASCH, JOHANNES-PETER, DE; STAHL, ELKE, DE; MUENTER, KLAUS, DE; LANG, DIETER, DE; EHMKE, HEIMO, DE

(73) Propriétaires(suite)/Owners(continued):BAYER SCHERING PHARMA AKTIENGESELLSCHAFT, DE

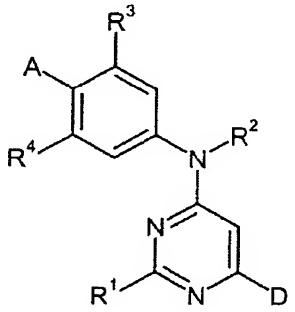
(74) Agent: FETHERSTONHAUGH & CO.

(57) Abrégé(suite)/Abstract(continued):
the invention relates to a compound of the formula (see formula I), in which R^1 represents amino or hydroxyl, R^2 represents hydrogen, (C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl, R^3 and R^4 independently of one another represent cyano, hydrogen, fluorine or chlorine, A represents a radical (see formula II), (see formula III) or (see formula IV) in which R^5 and R^6 independently of one another represent hydrogen, fluorine or chlorine, D (1) represents a radical selected from the group consisting of phenyl, etc; quinoline, etc; pyridylmethyl, etc; pyridyl, etc; etc or a salt, hydrate, hydrate of the salt or solvate thereof.

30725-332

Abstract

The invention relates to phenylaminopyrimidines and processes for their preparation, and to their use for preparing pharmaceuticals for the treatment and/or prophylaxis of diseases, in particular cardiovascular diseases. In a specific embodiment, the invention relates to a compound of the formula



(I),

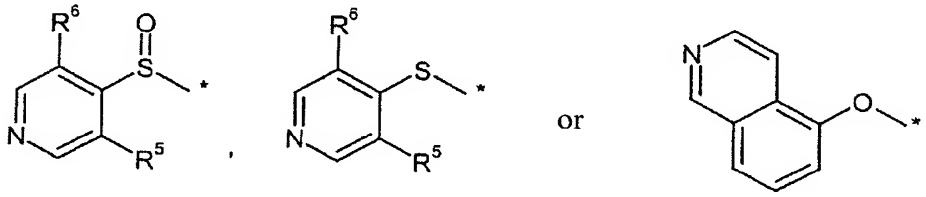
in which

R^1 represents amino or hydroxyl,

R^2 represents hydrogen, $(C_1$-$C_6)$-alkyl or $(C_3$-$C_8)$-cycloalkyl,

R^3 and R^4 independently of one another represent cyano, hydrogen, fluorine or chlorine,

A represents a radical



in which

R^5 and R^6 independently of one another represent hydrogen, fluorine or chlorine,

D (1) represents a radical selected from the group consisting of phenyl, etc; quinoline, etc; pyridylmethyl, etc; pyridyl, etc; etc

or a salt, hydrate, hydrate of the salt or solvate thereof.

30725-332

PHENYLAMINOPYRIMIDINES AND THEIR USE AS RHO-KINASE INHIBITORS

The invention relates to phenylaminopyrimidines, to a process for their preparation and to their use for preparing pharmaceuticals for the treatment and/or prophylaxis of diseases in humans and animals, in particular cardiovascular diseases.

An increase in the intracellular calcium concentration is one of the main factors triggering the contraction of the vascular musculature (Somlyo, A.P. and Himpens, B., *FASEB J.* 1989, 3, 2266-2276). This is effected primarily by agonists, such as, for example, phenylephrine or thromboxane A2 which, after stimulation of the phosphatidylinositol cascade, cause the release of calcium from the sarcoplasmatic reticulum. The elevated intracellular calcium activates the MLC kinase (myosin light-chain kinase) which phosphorylates the MLC subunits of the myosin molecule (Kamm, K.H. and Stull, J.T., *Annu. Rev. Pharmacol. Toxicol.* 1985, 25, 593-603). MLC phosphorylation induces the contraction of smooth muscles, MLC dephosphorylation after reduction of the intracellular calcium concentration results in the relaxation of the vessel.

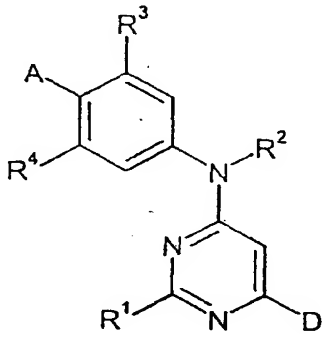
In addition to the calcium-dependent MLC phosphorylation, there is a further central, but calcium-independent regulation mechanism of the vascular tone. This is the Rho/Rho kinase signal path (Noda, M. et al., *FEBS Lett.* 1995, 367, 246-250; Uehata, M. et al., *Nature* 1997, 389, 990-994; Fukata, Y. et al., *Trends in Pharmacological Sciences* 2001, 22, 32-39). The binding of agonists such as, for example, phenylephrine or thromboxane A2 to their receptors results in the activation of the small G-proteins Rho which then interact with and activate Rho kinase. The activated Rho kinase inhibits myosin phosphatase following phosphorylation of a subunit of the enzyme. At the same time, Rho kinase phosphorylates MLC at the position which is also phosphorylated by MLC kinase. Inhibition of myosin phosphatase and phosphorylation of MLC induces the vascular musculature to contract. In contrast, inhibition of Rho kinase leads to a relaxation of the vessels. Accordingly, inhibitors of Rho kinase lower the blood pressure and increase coronary perfusion.

Compounds of a similar structure are known for other indications or other mechanisms of action. Thus, for example, US 3 478 030 and US 3 432 493 describe substituted aminopyrimidines capable of increasing coronary perfusion but acting as carboanhydrase inhibitors (J. Chem. Inf. Comp. Sciences 2002, 42, 94-102). Other pyrimidine derivatives have been described as anti-cancer and anti-HIV agents (Debi, M.; Indian J. Exp. Biol. 1997, 35, 1208-1213) or as cdk2 inhibitors (WO-A 01/64654).

It is an object of the present invention to provide pharmaceuticals for treating disorders, in particular cardiovascular disorders.

This object is achieved by the compounds of the formula (I), which act as Rho kinase inhibitors.

The present invention provides a compound of the formula (I)



(I),

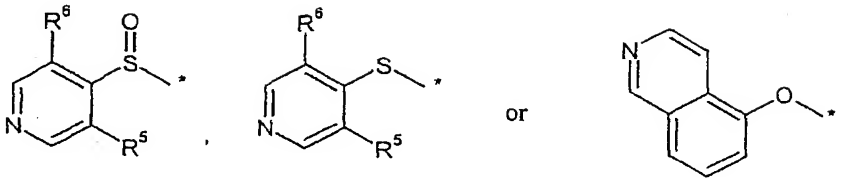
in which

R^1 represents amino or hydroxyl,

R^2 represents hydrogen, $(C_1\text{-}C_6)$-alkyl or $(C_3\text{-}C_8)$-cycloalkyl,

R^3 and R^4 independently of one another represent cyano, hydrogen, fluorine or chlorine,

A represents a radical



in which

R^5 and R^6 independently of one another represent hydrogen, fluorine or chlorine,

D (1) represents a radical selected from the group consisting of

phenyl, which for its part is substituted by $(C_1$-$C_4)$-alkyl-carbonylamino, hydroxymethyl, cyano, $(C_1$-$C_4)$-alkoxymethyl or 1,2-dioxymethylene,

quinoline, isoquinoline, indole or 6-membered heteroaryl having 2 or 3 nitrogen atoms, where the rings are in each case attached via a carbon atom,

pyridylmethyl, 2-oxo-2H-pyridin-1-yl, 4-oxo-4H-pyridin-1-yl, which for their part may be substituted by fluorine, chlorine or $(C_1$-$C_4)$-alkyl, and

pyridyl, which for its part is substituted by fluorine, chlorine or $(C_1$-$C_4)$-alkyl,

or

(2) represents a radical *-OR^7,

in which

R^7 represents phenyl which may be substituted by trifluoromethyl, trifluoromethoxy, nitro, cyano, *-NR^8R^9, fluorine, chlorine or 1,2-dioxymethylene or by (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, which for their part may be substituted by hydroxyl and/or *-NR^8R^9,

3- to 7-membered heterocyclyl having a nitrogen atom which may be substituted by hydrogen, (C_1-C_4)-alkyl or (C_3-C_8)-cycloalkyl,

5- or 6-membered heteroaryl having up to three nitrogen atoms,

(C_1-C_6)-alkyl or (C_3-C_7)-cycloalkyl which for their part may be substituted by hydroxyl or *-NR^8R^9,

thienyl, furyl, pyridylmethyl, naphthyl or benzyl,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl which for its part may be substituted by hydroxyl or amino, or

R^8 and R^9 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocycle which may have an additional oxygen atom or a group N-H or N-(C_1-C_4)-alkyl in the ring,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical *-$(CH_2)_x$-phenyl, where phenyl may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl, or represents *-$(CH_2)_y$-E,

in which

x represents 1, 2 or 3,

y represents 0, 1, 2 or 3 and

E represents pyrrolidine or piperidine, which for their part may be substituted by (C_1-C_4)-alkyl, or represents pyridyl which may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle which is substituted by *-$NR^{12}R^{13}$, 1,1-dioxyethylene, (C_1-C_4)-alkoxy, hydroxyl- or (C_1-C_4)-alkoxy-substituted (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl or 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

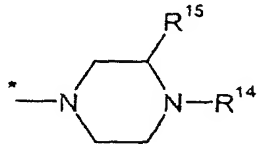
R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 7- to 12-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O in the ring and which may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl or benzyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a radical



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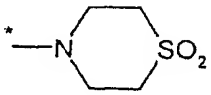


in which

R^{14} represents (C_2-C_6)-alkenyl, (C_1-C_4)-alkoxycarbonyl or *-$(CH_2)_z$-G,

in which

z represents 0 or 1 and

G represents (C_3-C_8)-cycloalkyl, pyridyl, optionally (C_1-C_4)-alkyl- or (C_1-C_4)-alkoxyl-substituted phenyl, tetrahydrofuran or 1,3-dioxolane,

and

R^{15} represents hydrogen or (C_1-C_4)-alkyl,

or a salt, hydrate, hydrate of the salt or solvate thereof.

The application also provides processes for preparing a compound as described herein, compositions comprising a compound as described herein, oral uses of a compound as described herein for the preparation of pharmaceuticals, and uses of the medicaments as described herein.

Depending on their structure, the compounds according to the invention can exist in stereoisomeric forms (enantiomers, diastereomers). Accordingly, the invention relates to the enantiomers or diastereomers and to their respective mixtures. The stereoisomerically uniform components can be isolated in a known manner from such mixtures of enantiomers and/or diastereomers.

Depending on the structure of the compounds, the invention also relates to tautomers of the compounds.

In the context of the invention, preferred salts are physiologically acceptable salts of the compounds according to the invention.

Physiologically acceptable salts of the compounds (I) include acid addition salts of mineral acids, carboxylic acids and sulphonic acids, for example salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid, toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds (I) also include salts of customary bases, such as, by way of example and by way of preference, alkali metal salts (for example sodium salts and potassium salts), alkaline earth metal salts (for example

calcium salts and magnesium salts) and ammonium salts, derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and by way of preference, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, dihydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine.

In the context of the invention, solvates are those forms of the compounds which, in solid or liquid state, form a complex by coordination with solvent molecules. Hydrates are a specific form of solvates where the coordination is with water.

In the context of the present invention, the substituents are as defined below, unless specified otherwise:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkanoyl, alkylcarbonylamino, alkoxycarbonyl and alkoxymethyl represent a linear or branched alkyl radical having generally 1 to 6, preferably 1 to 4, particularly preferably 1 to 3, carbon atoms, by way of example and by way of preference methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

By way of example and by way of preference, alkoxy represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

By way of example and by way of preference, alkanoyl represents acetyl and propanoyl.

By way of example and by way of preference, alkoxycarbonyl represents methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

By way of example and by way of preference, alkoxycarbonylamino represents methoxycarbonylamino, ethoxycarbonylamin, n-propoxycarbonylamino, isopropoxy-

carbonylamino, tert-butoxycarbonylamino, n-pentoxycarbonylamino and n-hexoxycarbonylamino.

Alkenyl represents a linear or branched alkenyl radical having generally 1 to 6 carbon atoms. Preference is given to a straight-chain or branched alkenyl radical having 2 to 4, particularly preferably 2 or 3, carbon atoms. The following radicals may be mentioned by way of example and by way of preference, vinyl, allyl, n-prop-1-en-1-yl and n-but-2-en-1-yl.

Cycloalkyl represents a cycloalkyl group having generally 3 to 8, preferably 5 to 7, carbon atoms, by way of example and by way of preference cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Heteroaryl represents an aromatic mono- or bicyclic radical having generally 5 to 10, preferably 5 or 6, ring atoms and up to 5, preferably up to 4, heteroatoms from the group consisting of S, O and N, by way of example and by way of preference thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl, isoquinolinyl.

Heterocyclyl represents a mono- or polycyclic, preferably mono- or bicyclic, non-aromatic heterocyclic radical having generally 4 to 12, preferably 5 to 8, ring atoms and up to 3, preferably up to 2, heteroatoms and/or hetero groups from the group consisting of N, O, S, SO, SO_2. The heterocyclyl radicals can be saturated or partially unsaturated. Preference is given to 5- to 8-membered monocyclic saturated heterocyclyl radicals having up to two heteroatoms from the group consisting of O, N and S, such as, by way of example and by way of preference, tetrahydrofuran-2-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolinyl, piperidinyl, morpholinyl, perhydroazepinyl.

A symbol * at a bond denotes the point of attachment in the molecule.

If radicals in the compounds according to the invention are substituted, the radicals can be mono- or polysubstituted by identical or different substituents unless

otherwise specified. A substitution by up to three identical or different substituents is preferred. Very particular preference is given to substitution with one substituent.

Preference is given to compounds of the formula (I)

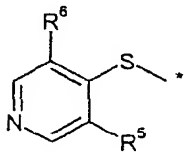
in which

R^1 represents amino,

R^2 represents hydrogen,

R^3 and R^4 independently of one another represent hydrogen, fluorine or chlorine,

A represents a radical



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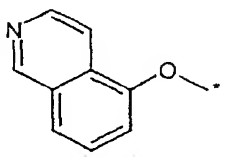


in which

R^5 and R^6 represent hydrogen,

D (1) represents a radical selected from the group consisting of

phenyl which is substituted by $(C_1$-$C_4)$-alkylcarbonylamino, hydroxymethyl, $(C_1$-$C_4)$-alkoxymethyl or 1,2-dioxymethylene,

quinoline, indole or 6-membered heteroaryl having 2 or 3 nitrogen atoms, where the rings are in each case attached via a carbon atom, pyridylmethyl, which may be substituted by $(C_1$-$C_4)$-alkyl,

and

pyridyl, which is substituted by (C_1-C_4)-alkyl,

or

(2) represents a radical *-OR^7,

in which

R^7 represents phenyl, which may be substituted by fluorine, chlorine, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy or 1,2-dioxymethylene,

(C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl, which for their part may be substituted by hydroxyl or *-NR^8R^9,

naphthyl or benzyl,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl or

R^8 and R^9 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocycle which may have an additional oxygen atom or a group N-H or N-(C_1-C_4)-alkyl in the ring,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical $*-(CH_2)_x$-phenyl, where phenyl may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl, or represents $*-(CH_2)_y-E$,

in which

x represents 1 or 2,

y represents 0, 1 or 2 and

E represents pyrrolidine or piperidine, which for their part may be substituted by (C_1-C_4)-alkyl, or represents pyridyl which may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle which is substituted by $*-NR^{12}R^{13}$, 1,1-dioxymethylene, (C_1-C_4)-alkoxymethyl or by 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)alkyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

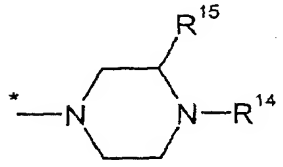
R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form an 8- to 10-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O in the ring and which may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, alkanoyl or benzyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a radical



,

in which

R^{14} represents (C_3-C_8)-cycloalkyl, (C_2-C_6)-alkenyl, (C_1-C_4)-alkoxycarbonyl or tetrahydrofuran-2-ylmethyl,

and

R^{15} represents hydrogen or (C_1-C_4)-alkyl,

and their salts, hydrates, hydrates of the salts and solvates.

Particular preference is given to compounds of the formula (I)

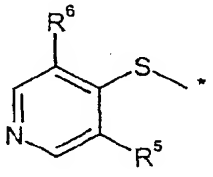
in which

R^1 represents amino,

R^2 represents hydrogen,

R^3 and R^4 independently of one another represent hydrogen, fluorine or chlorine,

A represents a radical



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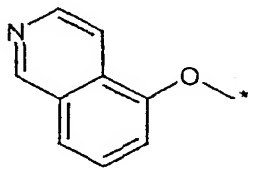


in which

R^5 and R^6 represent hydrogen,

D (1) represents a radical which is selected from the group consisting of

quinoline, indole, pyrazine, pyridazine and triazine, where the rings are in each case attached via a carbon atom,

or

(2) represents a radical *-OR^7

in which

R^7 represents phenyl which may be substituted by fluorine, chlorine, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy or 1,2-dioxymethylene,

(C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl which for their part may be substituted by hydroxyl or *-NR^8R^9,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl or

R^8 and R^9 together with the nitrogen atom to which they are attached form a morpholine or piperazine ring, where the second nitrogen atom of the piperazine ring may be substituted by (C_1-C_4)-alkyl,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical *-$(CH_2)_y$-E,

in which

y represents 0 or 1 and

E represents pyrrolidine or pyridyl, which for their part may be substituted by (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring which may be substituted by *-$NR^{12}R^{13}$, 1,1-dioxymethylene, (C_1-C_4)-alkoxymethyl or 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

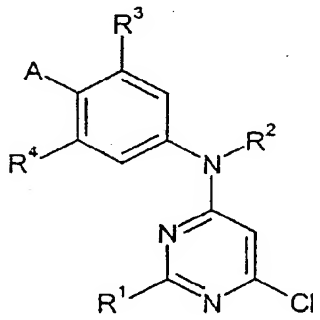
R^{10} and R^{11} together with the nitrogen atom to which they are attached form an 8- to 10-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O and which may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl or benzyl,

and their salts, hydrates, hydrates of the salts and solvates.

Very particular preference is given to combinations of two or more of the preferred ranges mentioned above.

The present invention also provides a process for preparing the compounds of the formula (I), which process is characterized in that either

[A] compounds of the formula (II)



(II),

in which

A, R^1, R^2, R^3 and R^4 are as defined above,

are reacted with compounds of the formula (III)

$$D\text{-}X^1 \qquad \text{(III)}$$

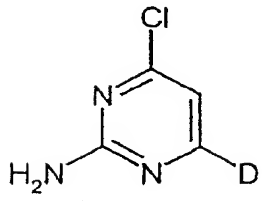
in which

D is as defined above and

X^1 represents hydrogen or *-$B(OH)_2$

or

[B] compounds of the formula (IV)

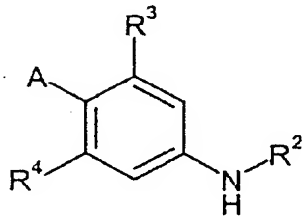


(IV),

in which

D is as defined above

are reacted with compounds of the formula (V)



(V),

in which

A, R^2, R^3 and R^4 are as defined above

to give compounds of the formula (I).

If X^1 represents hydrogen, the reaction in process step [A] is carried out in inert solvents or neat, if appropriate in the presence of a base, preferably in a temperature range of from 20°C to the reflux of the solvents or in the melt at atmospheric pressure.

Inert solvents are, for example, alcohols, such as methanol, ethanol, propanol, isopropanol or butanol, *N*-alkylated carboxamides, such as dimethylformamide or dimethylacetamide, alkyl sulphoxides, such as dimethyl sulphoxide, or other solvents, such as acetonitrile or pyridine, preferably ethanol or dimethylformamide.

Bases are, for example, alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide, or alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or amides, such as lithium diisopropylamide, or other bases, such as DBU, triethylamine or diisopropylethylamine, preferably diisopropylethylamine or triethylamine.

If X^1 represents *-$B(OH)_2$, the conversion into compounds of the formula (I) in process step [A] is generally carried out in inert solvents in the presence of a transition metal catalyst and in the presence of a base, preferably in the temperature range of from 70°C to 110°C at atmospheric pressure.

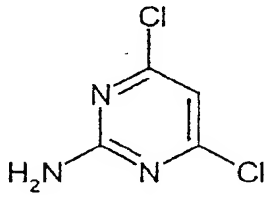
Inert solvents are, for example, ethers, such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, hydrocarbons, such as benzene, xylene or toluene, nitrated aromatic compounds, such as nitrobenzene, optionally *N*-alkylated carboxamides, such as dimethylformamide and dimethylacetamide, alkyl sulphoxides, such as dimethyl sulphoxide, or cyclic lactams, such as *N*-methylpyrrolidone. The solvents are, if appropriate, used with addition of ethanol. Preference is given to solvents from the group consisting of dimethylformamide, 1,2-dimethoxyethane and toluene/ethanol.

Preferred transition metal catalysts are palladium(0) or palladium(II) compounds, in particular bis(diphenylphosphaneferrocenyl)palladium(II) chloride, dichlorobis(triphenylphosphine)palladium or tetrakis(triphenylphosphine)palladium(0).

Preferred bases are potassium tert-butoxide, or alkali metal hydroxides or salts, such as potassium acetate, sodium hydroxide, sodium bicarbonate, sodium carbonate or potassium carbonate, if appropriate in the form of their aqueous solutions.

In process step [B], the conversion into compounds of the formula (I) is carried out in concentrated hydrochloric acid, preferably in a temperature range of from 70°C to 110°C at atmospheric pressure. In this reaction, the amino group at the pyrimidine may be hydrolyzed to the hydroxyl group.

To prepare compounds of the formula (II) for process step [A], compounds of the formula (V) are reacted with the compound of the formula (VI)

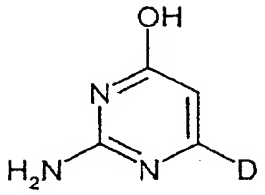


(VI)

under the reaction conditions described for process step [B].

In this reaction, the amino group at the pyrimidine may be hydrolyzed to the corresponding hydroxyl group.

To prepare compounds of the formula (IV) for process step [B], compounds of the formula (VII)



(VII),

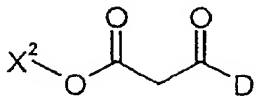
in which

D is as defined above

are reacted with phosphoryl chloride in N,N-dimethylaniline, preferably in a temperature range of from 70°C to 110°C at atmospheric pressure.

In another process variant, to prepare the compounds of the formula (IV), compounds of the formula (VI) are reacted with compounds of the formula (III) under the reaction conditions described for process step [A].

To prepare compounds of the formula (VII), compounds of the formula (VIII)



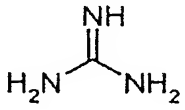
(VIII),

in which

D is as defined above and

X^2 represents alkyl, preferably methyl or ethyl,

are reacted with the compound of the formula (IX)



(IX).

The reaction of the compounds of the formula (VIII) and (IX) is initially carried out using concentrated hydrochloric acid in ethanol, preferably in a temperature range of from 50°C to the reflux of the solvents at atmospheric pressure, and then with aqueous sodium hydroxide solution, preferably in a temperature range of from 50°C to the reflux of the solvents at atmospheric pressure.

To prepare compounds of the formula (Va) for process step [B] in which R^2 represents (C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl, compounds of the formula (Vb) in which R^2 represents hydrogen

are reacted with compounds of the formula (X)

$$R^2\text{-}X^4 \qquad (X)$$

in which

R^2 represents (C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl and

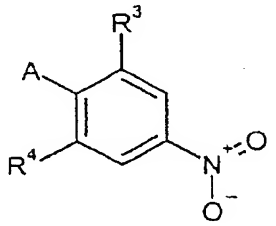
X^4 represents halogen, preferably bromine or chlorine.

The reaction is generally carried out in inert solvents, if appropriate in the presence of a base, preferably in a temperature range of from room temperature to the reflux of the solvents at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane or 1,2-dichloroethane, ethers, such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, or other solvents, such as acetone, dimethylformamide, dimethylacetamide, 2-butanone or acetonitrile, preferably tetrahydrofuran, methylene chloride, acetone 2-butanone, acetonitrile, dimethylformamide or 1,2-dimethoxyethane.

Bases are, for example, alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide, or sodium ethoxide or potassium ethoxide, or potassium tert-butoxide, or amides, such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or organometallic compounds, such as butyllithium or phenyllithium, or other bases, such as sodium hydride or DBU, preferably potassium tert-butoxide, caesium carbonate, DBU, sodium hydride, potassium carbonate or sodium carbonate.

To prepare the compounds of the formula (Vb) for process step [B] in which R^2 represents hydrogen, compounds of the formul;a (XI)



(XI),

in which

A, R^3 and R^4 are as defined above,

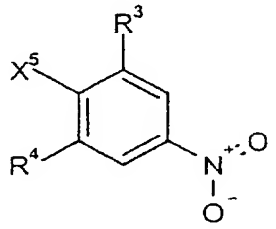
are reacted with reducing agents.

The reaction is generally carried out in inert solvents, if appropriate in the presence of hydrazine hydrate, preferably in a temperature range of from room temperature to the reflux of the solvents at from atmospheric pressure to 3 bar.

Reducing agents are for example, palladium on carbon and hydrogen, platinum oxide on carbon and hydrogen, tin dichloride or titanium trichloride, preferably palladium on carbon and hydrogen in the presence of hydrazine hydrate or platinum oxide on carbon and hydrogen.

Inert solvents are, for example, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or 2-ethylhexanol, hydrocarbons, such as benzene, xylene, toluene, hexane, cyclohexane or mineral oil fractions, or other solvents, such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine; preferred solvents are ethanol, n-butanol or 2-ethylhexanol.

To prepare the compounds of the formula (XI), compounds of the formula (XII)



(XII),

in which

R^3 and R^4 are as defined above and

X^5 represents halogen, preferably fluorine or chlorine,

are reacted with compounds of the formula (XIII)

A-H (XIII)

in which

A is as defined above.

The reaction is generally carried out in inert solvents, if appropriate in the presence of a base, preferably in a temperature range of from room temperature to the reflux of the solvents at atmospheric pressure.

Inert solvents are, for example, halogenated hydrocarbons, such as methylene chloride, trichloromethane or 1,2-dichloroethane, ethers, such as dioxane, tetrahydrofuran or 1,2-dimethoxyethane, or other solvents, such as acetone, dimethylformamide, dimethylacetamide, 2-butanone or acetonitrile, preferably acetonitrile, dimethylformamide or 1,2-dimethoxyethane.

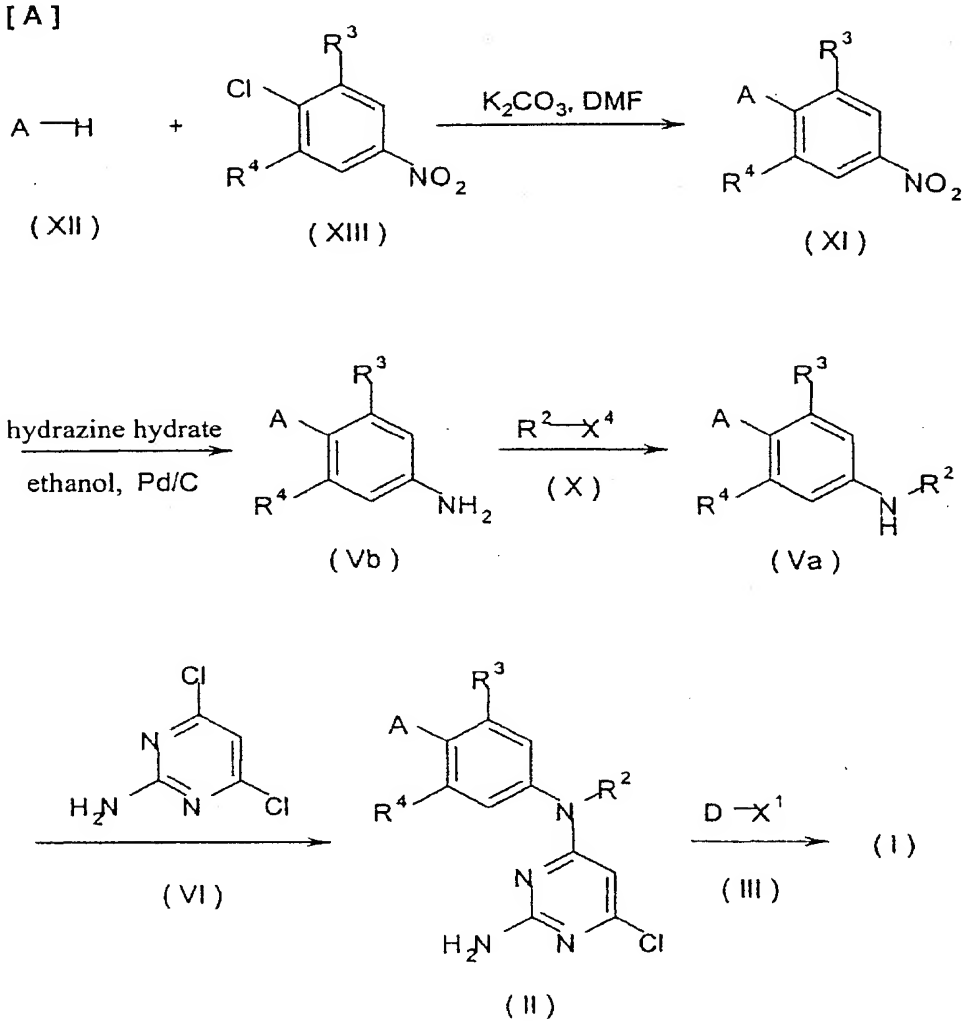
Bases are, for example, alkali metal carbonates, such as caesium carbonate, sodium carbonate or potassium carbonate, or sodium methoxide or potassium methoxide, or sodium ethoxide or potassium ethoxide, or potassium tert-butoxide, or amides, such as sodium amide, lithium bis(trimethylsilyl)amide or lithium diisopropylamide, or organometallic compounds, such as butyllithium or phenyllithium, or other bases, such as sodium hydride or DBU, preferably potassium tert-butoxide, caesium carbonate, potassium carbonate or sodium carbonate.

The compounds of the formulae (III), (VI), (VIII), (IX), (X), (XII) and (XIII) are known per se to the person skilled in the art or can be prepared by customary processes known from the literature.

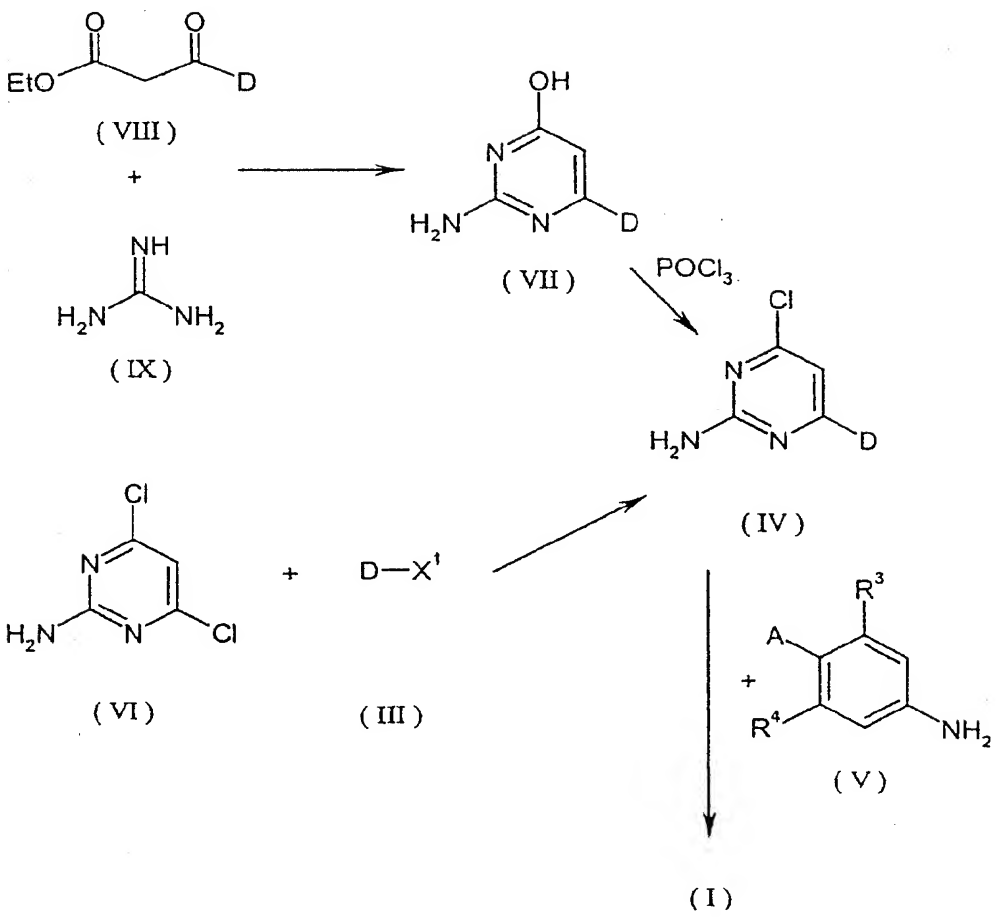
The compounds of the formula (I) can be derivatized further, for example by reaction with oxidizing agents.

The preparation of the compounds according to the invention can be illustrated by the reaction schemes below.

[A]



[B]



The compounds according to the invention have an unforeseeable useful spectrum of pharmacological and pharmacokinetic action. Accordingly, they are suitable for use as pharmaceuticals for the treatment and/or prophylaxis of diseases in humans and animals.

The pharmaceutic activity of the compounds of the formula (I) according to the invention can be explained by their action as Rho kinase inhibitors.

Owing to their pharmacological properties, the compounds of the formula (I) according to the invention can be used on their own or in combination with other active compounds for the treatment and/or prevention of disorders, in particular cardiovascular disorders.

The compounds of the formula (I) are suitable for the prophylaxis and/or treatment of cardiovascular disorders such as, for example, hypertension and cardiac insufficiency, stable and unstable angina pectoris, peripheral and cardiovascular disorders, of arrhythmias, of thromboembolic disorders and ischaemias, such as myocardial infarction, stroke, transitory and ischaemic attacks, obstruction of peripheral circulation, prevention of restenoses, such as, for example, after thrombolysis therapies, percutaneous transluminal angioplasties (PTA), percutaneous transluminal coronary angioplasties (PTCA), bypass, and for the prophylaxis and/or treatment of arteriosclerosis, asthmatic disorders and diseases of the urogenital system, such as, for example, prostate hypertrophy, erectile dysfunction, female sexual dysfunction, osteoporosis, gastroparesis and incontinence.

The present invention also relates to the use of the compounds of the formula (I) for preparing pharmaceuticals for the prophylaxis and/or treatment of the syndromes mentioned above.

The present invention furthermore relates to a method for the prophylaxis and/or treatment of the syndromes mentioned above using the compounds of the formula (I).

The present invention furthermore provides pharmaceuticals which comprise at least one compound according to the invention, preferably together with one or more pharmacologically acceptable auxiliaries or carriers, and their use for the purposes mentioned above.

The active compound can act systemically and/or locally. For this purpose, it can be administered in a suitable manner, such as, for example, orally, parenterally, pulmonarily, nasally, sublingually, lingually, buccally, rectally, transdermally, conjunctivally, otically, as stents or as an implant.

For these administration routes, the active compound can be administered in suitable administration forms.

For oral administration, known forms releasing the active compound rapidly and/or in modified form are suitable, such as, for example, tablets (non-coated and coated tablets, for example enterically coated tablets or film-coated tablets), capsules, sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, solutions and aerosols.

The parenteral administration can take place with circumvention of an absorbtion step (intravenous, intraarterial, intracardiac, intraspinal or intralumbar) or with involvement of an absorption (intramuscular, subcutaneous, intracutaneous, percutaneous or intraperitoneal). For parenteral administration, suitable administration forms are, inter alia, injection and infusion preparations in the form of solutions, suspensions, emulsions, lyophilizates and sterile powders.

For the other administration routes, for example, inhalation pharmaceutical forms (inter alia powder inhalers, nebulizers), nasal drops/solutions, sprays; tablets or capsules to be applied lingually, sublingually or buccally, suppositories, ear and eye preparations, gynocapsules, aqueous suspensions (lotions, shake lotions), lipophilic suspensions, ointments, creams, milk, pastes, dusting powder or implants are suitable.

The active compounds can be converted into the administration forms mentioned in a known manner. This takes place using inert non-toxic, pharmaceutically suitable auxiliaries. These include, inter alia, carriers (for example microcrystalline celluose), solvents (for example liquid polyethylene glycols), emulsifiers (for example sodium dodecylsulphate), dispersants (for example polyvinylpyrrolidone), synthetic and natural biopolymers (for example albumin), stabilizers (for example antioxidants such as ascorbic acid), colorants (for example inorganic pigments such as iron oxides) or taste and/or odour corrigents.

In general, it has been found to be advantageous both in human and in veterinary medicine to administer the active compound according to the invention in total amounts of from about 0.01 to about 700, preferably 0.01 to 100, mg/kg of body weight per 24 hours, if appropriate in the form of a plurality of individual doses, to

obtain the desired results. An individual dose contains the active compound according to the invention preferably in amounts of from about 0.1 to about 80, in particular 0.1 to 30, mg/kg of body weight.

In spite of this, it may be necessary, if appropriate, to deviate from the amounts mentioned, namely depending on the body weight, the route of application, the individual response to the active compound, the type of preparation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to use less than the abovementioned minimum amount, whereas in other cases the upper limit mentioned has to be exceeded. In the case of the administration of relatively large amounts, it may advisable to divide these into several individual administrations over the course of the day.

The percentages in the tests and examples below are, unless indicated otherwise, percentages by weight; parts are parts by weight. Solvent ratios, dilution ratios and concentrations of liquid/liquid solutions are in each case based on the volume.

A. Examples

Abbreviations

TLC	thin-layer chromatography
DCI	direct chemical ionization (in MS)
DCM	dichloromethane
DIEA	*N,N*-diisopropylethylamine
DMSO	dimethyl sulphoxide
DMF	*N,N*-dimethylformamide
EA	ethyl acetate
EI	electron impact ionization (in MS)
ESI	electrospray ionization (in MS)
m.p.	melting point
sat.	saturated
h	hour
HPLC	high-pressure, high-performance liquid chromatography
conc.	concentrated
LC-MS	liquid-chromatography-coupled mass spectroscopy
LDA	lithium diisopropylamide
MPLC	medium-pressure, medium-performance liquid chromatography
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
RP-HPLC	reverse phase HPLC
RT	room temperature
R_f	retention index (in TLC)
R_t	retention time (in HPLC)
THF	tetrahydrofuran

HPLC, LCMS and GCMS methods:

Method 1 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil* RP-18, 60 mm × 2 mm, 3.5 µm; mobile phase: A=5 ml of $HClO_4$/l of H_2O, B=acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 6.5 min 90% B; flow rate: 0.75 ml/min; temp.: 30°C; detection UV 210 nm.

Method 2 (HPLC):

Instrument: HP 1100 with DAD detection; column: Kromasil RP-18, 60 mm × 2 mm, 3.5 µm; mobile phase: A=5 ml of $HClO_4$/l of H_2O, B=acetonitrile; gradient: 0 min 2% B, 0.5 min 2% B, 4.5 min 90% B, 9 min 90% B; flow rate: 0.75 ml/min; temp.: 30°C; detection UV 210 nm.

Method 3 (HPLC):

Instrument: Finnigan* MAT 900S, TSP: P4000,AS3000,UV3000HR; column: Symmetry* C 18, 150 mm × 2.1 mm, 5.0 µm; mobile phase C: water, mobile phase B: water + 0.3 g of 35% strength HCl, mobile phase A: acetonitrile; gradient: 0.0 min 2% A → 2.5 min 95% A → 5 min 95% A; oven: 70°C; flow rate: 1.2 ml/min; UV detection: 210 nm.

Method 4 (LCMS):

Instrument: Micromass Quattro* LCZ, HP1100; column: Symmetry C18, 50 mm × 2.1 mm, 3.5 µm; mobile phase A: acetonitrile + 0.1% formic acid, mobile phase B: water + 0.1% formic acid; gradient: 0.0 min 10% A → 4.0 min 90% A → 6.0 min 90% A; oven: 40°C; flow rate: 0.5 ml/min; UV detection: 208-400 nm.

Method 5 (LCMS):

Instrument: Micromass Platform* LCZ, HP1100; column: Symmetry C18, 50 mm × 2.1 mm, 3.5 µm; mobile phase A: acetonitrile + 0.1% formic acid, mobile phase B: water + 0.1% formic acid; gradient: 0.0 min 10% A → 4.0 min 90% A → 6.0 min 90% A; oven 40°C; flow rate: 0.5 ml/min; UV detection: 208-400 nm.

*Trade-mark

Method 6 (LCMS):

Instrument MS: Micromass ZQ; instrument HPLC: Waters Alliance* 2790; column: Symmetry C 18, 50 mm × 2.1 mm, 3.5 µm; mobile phase B: acetonitrile + 0.05% formic acid, mobile phase A: water + 0.05% formic acid; gradient: 0.0 min 10% B → 3.5 min 90% B → 5.5 min 90% B; oven: 50°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 7 (LCMS):

Instrument: Micromass Platform LCZ, HP1100; column: Symmetry C18, 50 mm × 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B: acetonitrile + 0.05% formic acid; gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; oven: 40°C; flow rate: 0.5 ml/min; UV detection: 208-400 nm.

Method 8 (LCMS):

Instrument: Micromass Quattro LCZ, HP1100; column: Symmetry C18, 50 mm × 2.1 mm, 3.5 µm; mobile phase A: water + 0.05% formic acid, mobile phase B: acetonitrile + 0.05% formic acid; gradient: 0.0 min 90% A → 4.0 min 10% A → 6.0 min 10% A; oven: 40°C; flow rate: 0.5 ml/min; UV detection: 208-400 nm.

Method 9 (GCMS):

Column: HP-5 30 m × 320 µm × 0.25 µm (thickness of the film); carrier gas: helium; temperature gradient: 14°C/min up to 300°C, then 1 min const. 300°C; flow rate: 1.5 ml/min; initial temperature: 60°C; starting time: 2 min; front injector temp.: 250°C.

Method 10 (HPLC):

Instrument: Waters Alliance 2790 LC; column: Symmetry C18, 50 mm × 2.1, 3.5 µm; mobile phase A: water + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid; gradient: 0.0 min 5% B → 5.0 min 10% B → 6.0 min 10% B; temperature: 50°C; flow rate: 1.0 ml/min; UV detection: 210 nm.

*Trade-mark

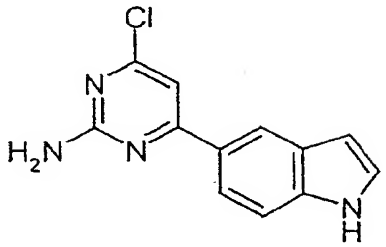
Method 11 (chiral HPLC):

Column: chiral stationary phase, based on the optically active monomer N-methacrylacyl-L-leucine-dicyclopropylmethylamide; mobile phase A: isohexane, mobile phase B: ethyl acetate; gradient: A:B → 20:80; flow rate: 15 ml/min.

Starting materials

Example I

4-Chloro-6-(1H-indol-5-yl)-2-pyrimidinamine



380 mg (2.33 mmol) of 2-amino-4,6-dichloropyrimidine are suspended in 20 ml of toluene and 10 ml of ethanol, and 80 mg (0.07 mmol) of tetrakis(triphenylphosphine)palladium(0) are added. After 20 minutes of stirring at room temperature, 450 mg (2.80 mmol) of 5-indoleboronic acid and 3.90 ml of a 2M sodium carbonate solution are added. The mixture is stirred at 120°C for 20 hours. After cooling, the reaction solution is neutralized using 1N hydrochloric acid and extracted three times with in each case 50 ml of ethyl acetate. The organic phase is dried over sodium sulphate, filtered off and concentrated under reduced pressure. The crude product is purified chromatographically on silica gel 60 (mobile phase: cyclohexane → cyclohexane: ethyl acetate 1:1).

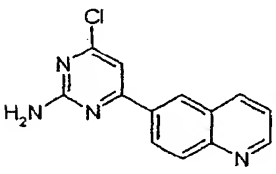
This gives 32 mg (4% of theory) of product.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.47 (s, 1H), 7.33 (s, 1H), 7.50 (dd, 2H), 7.98 (s, 1H), 11.13 (s, 1H)

MS (ESIpos): m/z = 245 $(M+H)^+$

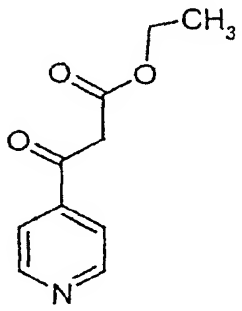
HPLC (method 1): R_t = 4.12

The example listed in the table below can be prepared analogously to the procedure described for Example I using the appropriate starting materials.

Example	Structure	Analytical data
II		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.24 (br.s, 2H), 7.44 (s, 1H), 7.61 (dd, 1H), 8.12 (d, 1H), 8.45 (dt, 2H), 8.77 (d, 1H), 8.98 (dd, 1H) MS (ESIpos): m/z = 257 $(M+H)^+$ HPLC (method 1): R_t = 3.54 min

Example III

Ethyl 3-oxo-3-(4-pyridinyl)propanoate



25 g (203 mmol) of isonicotinic acid, 35.12 g (243.7 mmol) of 2,2-dimethyl-1,3-dioxolane-4,6-dione and 49.6 g (406 mmol) of 4-dimethylaminopyridine are initially charged in 300 ml of dichloromethane and cooled to 0°C. A 1N solution of 46.1 g (223.4 mmol) of 1,3-dicyclohexylcarbodiimide in dichloromethane is added dropwise. The mixture is stirred at room temperature for 2 hours. The resulting precipitate is filtered off and washed with dichloromethane. The filtrate is concentrated under reduced pressure. The residue is dissolved in 1200 ml of ethanol, a solution of 96.6 g (507.7 mmol) of p-toluenesulphonic acid monohydrate in 300 ml of ethanol is added and the mixture is stirred under reflux for one hour. After cooling, the ethanol is removed under reduced pressure. The residue is taken up in 1000 ml of ethyl acetate and 900 ml of water and dissolved by heating. The organic phase is separated off, washed with 600 ml of saturated sodium bicarbonate solution

and saturated sodium chloride solution and dried over sodium sulphate. The solution is concentrated under reduced pressure. The crude product is filtered through a silica gel frit using dichloromethane:methanol 10:1. Since the aqueous phase still contains some product, it is extracted with dichloromethane and the extract is dried over sodium sulphate and concentrated under reduced pressure. The crude product is filtered through a silica gel frit using dichloromethane:methanol 10:1.

This gives a total of 25.9 g (42% of theory) of product.

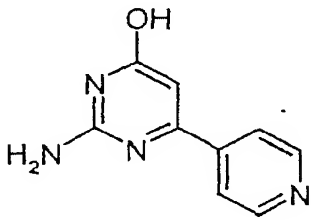
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.17 (t, 3H), 4.12 (q, 2H), 4.25 (s, 2H), 7.82 (dd, 2H), 8.83 (dd, 2H)

LC-MS (method 3): R_t = 2.40 min

MS (ESIpos): m/z = 194 $(M+H)^+$

Example IV

2-Amino-6-(4-pyridinyl)-4-pyrimidinol



25 g (81.52 mmol) of the compound from Example III and 13.22 g (73.37 mmol) of guanidinium carbonate are dissolved in 250 ml of ethanol, concentrated hydrochloric acid is added and the mixture is stirred under reflux overnight. After cooling, the precipitate is filtered off with suction, washed with ethanol and dried under high vacuum. 250 ml of 1N sodium hydroxide solution are added to the solid, and the mixture is stirred under reflux for 2 hours. After cooling, the mixture is acidified using concentrated acetic acid and the precipitated product is filtered off with suction and washed with diethyl ether.

Drying under high vacuum gives 12.52 g (82% of theory) of product.

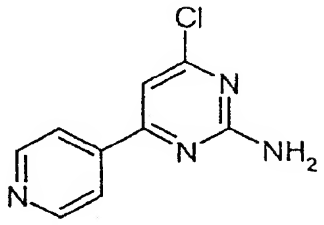
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.23 (s, 1H), 6.89 (br.s, 2H), 7.86 (dd, 2H), 8.64 (dd, 2H)

LC-MS (method 4): R_t = 0.30 min

MS (ESIpos): m/z = 189 $(M+H)^+$

Example V

4-Chloro-6-(4-pyridinyl)-2-pyrimidinamine



10.4 g (55.26 mmol) of the compound from Example IV are dissolved in 28.33 ml (303.95 mmol) of phosphoryl chloride. 0.88 g (7.18 mmol) of N,N-dimethylaniline are slowly added dropwise, and the mixture is stirred at 100°C for one hour. The reaction solution is then stirred at room temperature for another 2 hours. The phosphoryl chloride is removed under reduced pressure using a rotary evaporator. Water:dichloromethane 9:1 is added to the residue, and the mixture is boiled for 5 minutes. The mixture is then neutralized using saturated sodium bicarbonate solution and the product is filtered off with suction and dried under high vacuum.

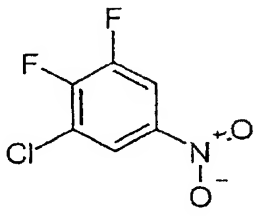
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.31 (br.s, 2H), 7.38 (s, 1H), 8.00 (dd, 2H), 8.74 (dd, 2H)

LC-MS (method 4): R_t = 1.08 min

MS (ESIpos): m/z = 207 $(M+H)^+$

Example VI

1-Chloro-2,3-difluoro-5-nitrobenzene

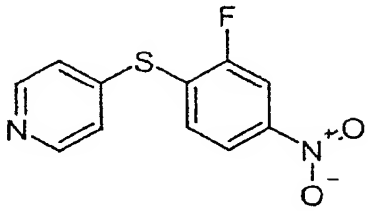


The compound can be obtained by oxidizing 3-chloro-4,5-difluoroaniline, described in JP 05059067, with hydrogen peroxide in trifluoroacetic acid according to a

process described in Heaton, A. et al., J. Fluorine Chem. 1997, 81 (2), 133-138 and Krapcho, A.P. et al., J. Org. Chem. 1990, 55 (21), 5662-5664 for the preparation of analogous derivatives.

Example VII

4-[(2-Fluoro-4-nitrophenyl)sulphanyl]pyridine



21 g (188.9 mmol) of 4-mercaptopyridine, 30.05 g (188.9 mmol) of 3,4-difluoronitrobenzene and 60.05 g (434.5 mmol) of potassium carbonate are dissolved in dimethylformamide, and the mixture is stirred at 40°C for 3 hours. The reaction solution is then diluted with 500 ml of ethyl acetate and 300 ml of water. The aqueous phase is extracted five times with in each case 100 ml of ethyl acetate. The combined organic phases are washed with 200 ml of saturated sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure using a rotary evaporator. The residue is purified by MPLC (mobile phase: ethyl acetate:cyclohexane 1:1).

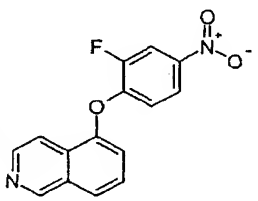
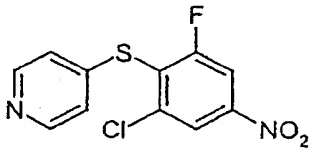
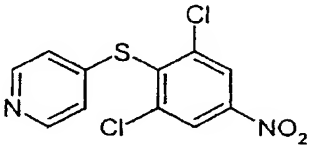
This gives 37.3 g (79% of theory) of product.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.28 (dd, 2H), 7.79 (t, 1H), 8.15 (dd, 1H), 8.30 (dd, 1H), 8.50 (dd, 2H)

LC-MS (method 4): R_t = 2.68 min

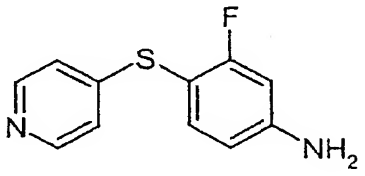
MS (ESIpos): m/z = 251 $(M+H)^+$

The examples listed in the table below can be prepared from the appropriate mercapto or hydroxy heterocycles and their corresponding 4-fluoro- and 4-chloronitrobenzene derivatives, analogously to the procedure described in Example VII.

Example	Structure	Analytical data
VIII		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.14 (t, 1H), 7.55 (d, 1H), 7.74 (t, 1H), 7.86 (d, 1H), 8.08 (t, 2H), 8.43 (dd, 1H), 8.58 (d, 1H), 9.46 (s, 1H) HPLC (method 1): R_t = 3.80 min
IX		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.15 (dd, 2H), 8.37 (dd, 1H), 8.41- 8.45 (m, 3H) HPLC (method 1): R_t = 3.77 min MS (CIpos): m/z = 302 $(M+NH_4)^+$
X		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 7.07 (dd, 2H), 8.41 (dd, 2H), 8.54 (s, 2H) HPLC (method 1): R_t = 3.92 min MS (ESIpos): m/z = 301 (M+H)+

Example XI

3-Fluoro-4-(4-pyridinylsulphanyl)aniline



37 g (147.9 mmol) of the compound from Example VII are dissolved in 1000 ml of ethanol, and 143.86 ml (2.95 mol) of hydrazine hydrate and 4 g of palladium on carbon are added. The reaction mixture is stirred under reflux overnight. After cooling, the mixture is filtered off with suction through silica gel, and the filter cake is washed with ethanol. The filtrate is concentrated under reduced pressure using a rotary evaporator. The residue is suspended in diethyl ether and filtered off with suction. The precipitate is then suspended in water and filtered off with suction. The product is washed two more times with a little water.

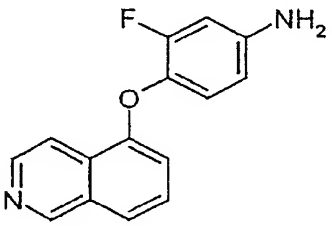
Drying under high vacuum gives 27.3 g (84% of theory) of product.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.02 (br.s, 2H), 6.49-6.54 (m, 2H), 6.93 (dd, 2H), 7.23 (t, 1H), 8.32 (dd, 2H)

LC-MS (method 4): R_t 0.96 min

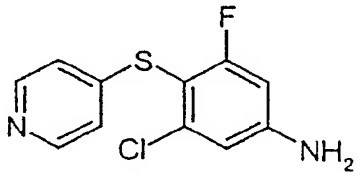
MS (ESIpos): m/z = 221 $(M+H)^+$

The example listed in the table below can be prepared analogously to the procedure described for Example XI from the appropriate starting materials.

Example	Structure	Analytical data
XII		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 5.46 (br.s, 2H), 6.46 (d, 1H), 6.55 (dd, 1H), 6.85 (d, 1H), 7.04 (t, 1H), 7.54 (t, 1H), 7.77 (d, 1H), 8.10 (d, 1H), 8.58 (d, 1H), 9.35 (s, 1H) LC-MS (method 4): R_t = 1.95 min MS (ESIpos): m/z = 255 $(M+H)^+$

Example XIII

3-Chloro-5-fluoro-4-(4-pyridinylsulphanyl)aniline



3.19 g (11.205 mmol) of the compound from Example IX are dissolved in 200 ml of ethanol. 638 mg (2.81 mmol) of platinum(IV) oxide are then added, and the mixture is stirred at RT and atmospheric pressure under an atmosphere of hydrogen for 2 hours. For work-up, the reaction solution is filtered off with suction through

kieselguhr and washed thoroughly with ethanol. The filtrate is concentrated under reduced pressure.

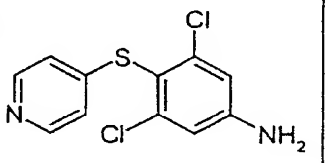
This gives 2.755 g (81% of theory) of product.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.37 (s, 2H), 6.49 (dd, 1H), 6.72-6.74 (m, 1H), 6.93 (dd, 2H), 8.34 (dd, 2H)

HPLC (method 1): R_t = 3.68 min

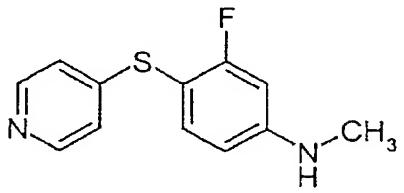
MS (ESIpos): m/z = 255 $(M+H)^+$

The example listed in the table below can be prepared analogously to the procedure described for Example XIII from the appropriate starting materials.

Example	Structure	Analytical data
XIV		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.32 (s, 2H), 6.83 (s, 2H), 6.90 (dd, 2H), 8.33 (dd, 2H). HPLC (method 1): R_t = 3.80 min MS (ESIpos): m/z = 270.9 $(M+H)^+$

Example XV

3-Fluoro-N-methyl-4-(4-pyridinylsulphanyl)aniline



440.5 mg (2 mmol) of the compound from Example XI are dissolved in 2 ml of methanol, and 2 ml of a 21% strength sodium ethoxide solution are added. 84 mg (2.8 mmol) of paraformaldehyde are added, and the mixture is stirred at room temperature overnight. 75.7 mg (2 mmol) of sodium borohydride are added to the

reaction mixture, which is then heated under reflux for 1.5 hours. After cooling, the mixture is carefully hydrolysed using 1M potassium hydroxide solution. Once the reaction has stopped, the resulting solid is filtered off with suction and washed with a large quantity of water. The solid residue is dissolved in diethyl ether, dried over sodium sulphate and concentrated under reduced pressure using a rotary evaporator.

This gives 387 mg (83% of theory) of product.

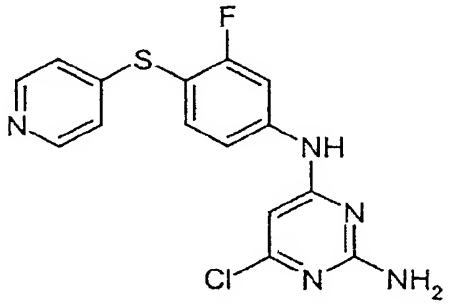
^{1}H-NMR (200 MHz, DMSO-d_6): δ = 2.73 (d, 3H), 6.45-6.52 (m, 2H), 6.59-6.69 (m, 1H), 6.92 (dd, 2H), 7.29 (t, 1H), 8.32 (dd, 2H)

LC-MS (method 4): R_t = 2.35 min

MS (ESIpos): m/z = 235 $(M+H)^+$

Example XVI

N-(2-Amino-6-chloro-4-pyrimidinyl)-N-[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]-amine



2.98 g (18.16 mmol) of 2-amino-4,6-dichloropyrimidine are suspended in 300 ml of water, and 4 g (18.16 mmol) of the compound from Example XI and 1.82 ml of concentrated hydrochloric acid are then added. The mixture is stirred at 100°C overnight. For work-up, the reaction solution is allowed to cool and made alkaline using saturated sodium bicarbonate solution. The precipitated product is filtered off with suction and then dried in a vacuum drying cabinet at 40°C.

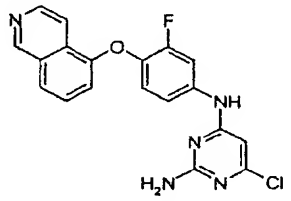
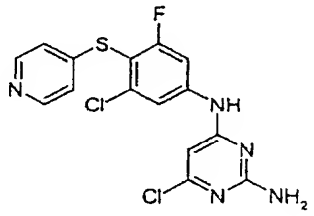
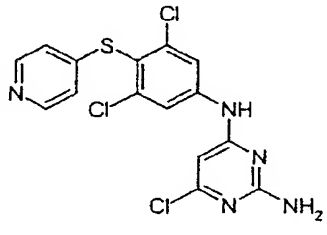
This gives 6.04 g (74% of theory) of product.

^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.09 (s, 1H), 6.99 (dd, 4H), 7.41 (dd, 1H), 7.56 (dd, 1H), 8.27 (dd, 1H), 8.36 (dd, 2H), 9.89 (s, 1H)

HPLC (method 1): R_t = 3.69 min

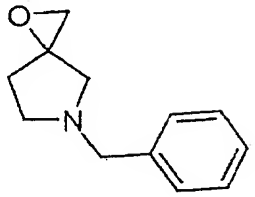
MS (ESIpos): m/z = 348 $(M+H)^+$

The examples listed in the table below can be prepared analogously to the procedure described above for Example XVI from the appropriate starting materials.

Example	Structure	Analytical data
XVII		LC-MS (method 3): R_t = 1.95 min MS (ESIpos): m/z = 382 $(M+H)^+$
XVIII		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.08 (s, 1H), 7.00 (d, 2H), 7.09 (s, 2H), 7.74 (s, 1H), 8.15 (dd, 1H), 8.37 (dd, 2H), 10.00 (s, 1H) HPLC (method 1): R_t = 3.81 min MS (ESIpos): m/z = 382 $(M+H)^+$
XIX		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 6.34 (s, 1H), 7.69 (d, 2H), 8.36 (s, 2H), 8.71 (d, 2H), 10.72 (s, 1H). HPLC (method 1): R_t = 3.8 min MS (ESIpos): m/z = 398 $(M+H)^+$

Example XX

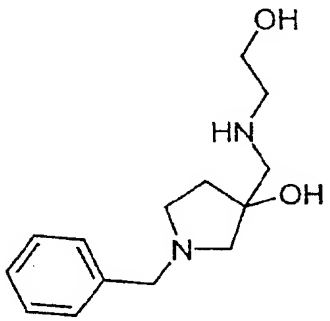
5-Benzyl-1-oxa-5-azaspiro[4.2]heptane



The compound can be prepared from N-benzyl-3-pyrrolidinone by a procedure of E.J. Corey et al. according to US 4,508,724.

Example XXI

1-Benzyl-3-hydroxy-3-(2-hydroxyethylaminomethyl)pyrrolidine

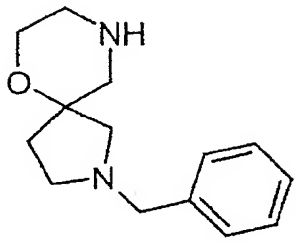


32.7 g (0.17 mol) of Example XX are added dropwise to 31 g (0.52 mol) of ethanolamine in 250 ml of water, and the mixture is stirred at room temperature overnight. The mixture is extracted with diethyl ether, the aqueous phase is concentrated and the residue is distilled under high vacuum.

This gives 42.1 g (96% of theory) of product.
Boiling point: 180-190°C/0.1 mbar

Example XXII

7-Benzyl-1-oxa-4,7-diazaspiro[5.4]decane



85 g (340 mmol) of Example XXI are dissolved in a mixture of 280 ml of concentrated sulphuric acid and 140 ml of water, and the mixture is heated at 180°C overnight. The mixture is made alkaline using 45% strength aqueous sodium hydroxide solution, precipitated salts are dissolved in water and the mixture is extracted five times with in each case 200 ml of chloroform. The organic phases are dried over potassium carbonate, the drying agent is separated off and the solution is concentrated.

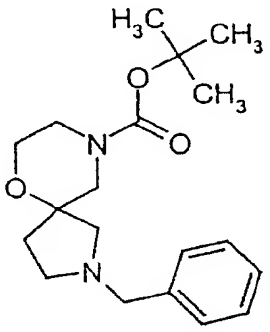
The residue is distilled under high vacuum.

This gives 60 g (76% of theory) of product.

Boiling point: 125°C/0.08 mbar

Example XXIII

tert-Butyl 7-benzyl-1-oxa-4,7-diazaspiro[5.4]decane-4-carboxylate



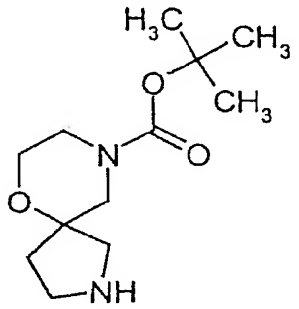
2 g of sodium hydroxide pellets in 25 ml of water are added to 10.3 g (47 mmol) of Example XXII in 30 ml of tert-butanol, and 11 g (50 mmol) of di-tert-butyl pyrocarbonate are added dropwise. The mixture is stirred at room temperature overnight, 50 ml of water are added, the mixture is extracted three times with

chloroform, the extract is dried over potassium carbonate, the drying agent is filtered off with suction, the filtrate is concentrated and the residue is distilled under high vacuum.

This gives 13.8 g (88% of theory) of product.
Boiling point: 160°C/0.3 mbar

Example XXIV

tert-Butyl 1-oxa-4,7-diazaspiro[5.4]decane-4-carboxylate

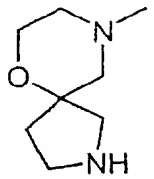


13.7 g (41 mmol) of Example XXIII are dissolved, 3 g of 10% palladium on carbon are added and the mixture is hydrogenated at 100°C and 100 bar. The catalyst is filtered off with suction, the filtrate is concentrated and the residue is distilled under high vacuum.

This gives 7.6 g (75% of theory) of product.
Boiling point: 113°C/0.07 mbar

Example XXV

9-Methyl-6-oxa-2,9-diazaspiro[4.5]decane

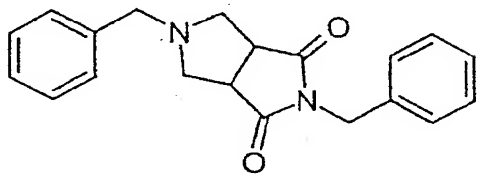


The compound can be prepared from Example XXII by reductive alkylation according to the method described for the preparation of Example XV, followed by

hydrogenolytic cleavage of the benzyl group according to the method described for the preparation of Example XXIV.

Example XXVI

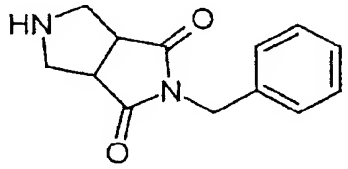
3,7-Dibenzyl-3,7-diazabicyclo[3.3.0]octane-2,4-dione



18.7 g (0.1 mol) of N-benzylmaleimide, 25 g (0.15 mol) of N-benzylglycine and 5 g (0.157 mol) of paraformaldehyde are heated under reflux in 500 ml of toluene until the evolution of CO_2 has ended. The mixture is concentrated and the crude product is used without further purification.

Example XXVII

3-Benzyl-3,7-diazabicyclo[3.3.0]octane-2,4-dione



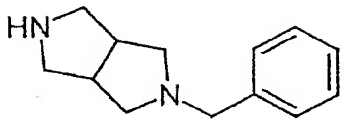
150 g (0.4 mol) of the crude product from Example XXVI in 750 ml of ethanol are hydrogenated on 15 g of 10% palladium on carbon at 100°C and 100 bar. The catalyst is filtered off and the solution is concentrated and filtered through 1.2 kg of silica gel using dichloromethane.

This gives 38 g (42% of theory) of product.

R_f value: 0.35 (mobile phase: dichloromethane 96%/methanol 4%).

Example XXVIII

3-Benzyl-3,7-diazabicyclo[3.3.0]octane

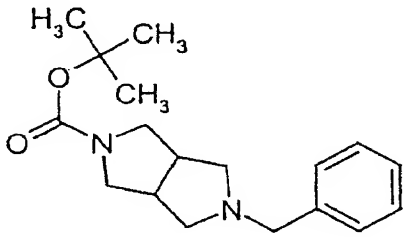


16 g (0.42 mol) of lithium aluminium hydride are initially charged in 350 ml of absolute tetrahydrofuran, and 38 g (0.165 mol) of Example XXVII in 150 ml of absolute tetrahydrofuran are added dropwise. The mixture is heated under reflux for another five hours, 16 ml each of water, 16% strength aqueous potassium hydroxide solution and again water are added dropwise and the inorganic salts are filtered off with suction and decocted twice with tetrahydrofuran. The filtrates are concentrated and distilled under membrane-pump vacuum.

This gives 31.4 g (94% of theory) of product.
Boiling point: 140°C/4 mbar

Example XXIX

tert-Butyl 7-benzyl-3,7-diazabicyclo[3.3.0]octane-3-carboxylate

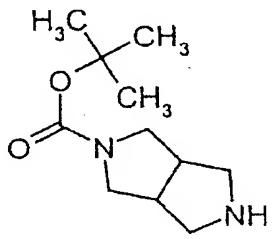


6 g (29.7 mmol) of Example XXVIII are initially charged, 1.4 g (35 mmol) of sodium hydroxide in 30 ml of water are added and 8 g (36.7 mmol) of tert-butyl pyrocarbonate are then added dropwise. The mixture is stirred at room temperature overnight and then extracted with chloroform, the extract is dried over potassium carbonate, the drying agent is filtered off, the filtrate is concentrated and the residue is distilled.

This gives 7.6 g (75% of theory) of product.
Boiling point: 153-156°C/0.2 mbar

Example XXX

tert-Butyl 3,7-diazabicyclo[3.3.0]octane-3-carboxylate



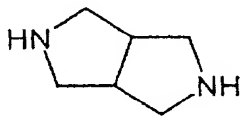
7.6 g (25.3 mmol) of Example XXIX in 100 ml of ethanol are hydrogenated on 1.5 g of 10% palladium/carbon at 100°C and 100 bar. The catalyst is filtered off, the filtrate is concentrated and the residue is distilled.

This gives 3.6 g (76% of theory) of product.

Boiling point: 92°C/0.08 mbar

Example XXXI

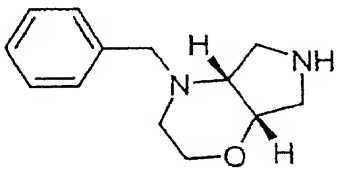
3,7-Diazabicyclo[3.3.0]octane



The compound can be prepared from Example XXX by removing the tert-butoxycarbonyl group with hydrogen chloride (4 M in dioxane) or with trifluoroacetic acid/dichloromethane (1:1).

Example XXXII

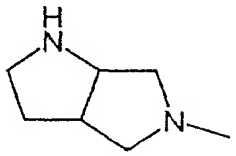
(4aR,7aS)-4-Benzyloctahydropyrrolo[3,4-b][1,4]oxazine



The preparation of the compound is described in US 6 004 956.

Example XXXIII

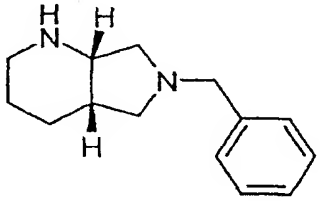
5-Methyloctahydropyrrolo[3,4-b]pyrrole



The preparation of the compound is described in DE-A 4 032 560.

Example XXXIV

[S,S]-8-Benzyl-2,8-diazabicyclo[4.3.0]nonane



3 g (20 mmol) of D-(-)-tartaric acid are dissolved in 10 ml of dimethylformamide by heating at 80°C, and a solution of 2.16 g (10 mmol) of cis-8-benzyl-2,8-diazabicyclo[4.3.0]nonane in 3 ml of dimethylformamide is added. The mixture is stirred at 0°C for 1 hour and then filtered off with suction, and the product is washed with dimethylformamide and methoxyethanol. (Yield: 1.93 g)

Melting point: 146-151°C

$[\alpha]_D^{24}$ = -19.3° (c=1, H_2O)

One recrystallization from methoxyethanol gives diastereomerically pure [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane D-tartrate.

Melting point: 148-154°C

$[\alpha]_D^{24}$ = -22.7° (c=1, H_2O)

40 g of the salt are dissolved in 250 ml of water, and 32 g of 45% strength aqueous sodium hydroxide solution are added. The oil that has separated off is taken up in 150 ml of tert-butyl methyl ether and the aqueous phase is re-extracted with 150 ml

of tert-butyl methyl ether. The organic phases are combined and, after drying over sodium sulphate, concentrated. The residue is then distilled under reduced pressure.

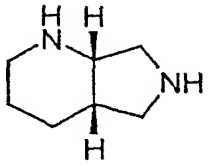
This gives 18.5 g of product.

Boiling point: 107-109°C/0.1 mbar

$[\alpha]_D^{24} = 17.3°$ (undiluted)

Example XXXV

[S,S]-2,8-Diazabicyclo[4.3.0]nonane



28.4 g (0.131 mol) of [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane in 190 ml of methanol are hydrogenated over 5.8 g of palladium on carbon (5%) at 90°C and 90 bar for 5 hours. The catalyst is then filtered off with suction and washed with methanol and the filtrate is concentrated under reduced pressure. The residue is distilled without fractionation.

This gives 15 g (91% of theory) of product.

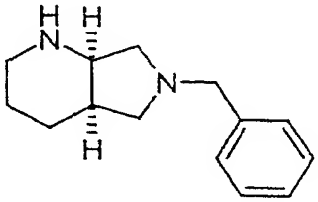
Boiling point: 44-59°C/0.18 mbar

$[\alpha]_D^{24} = -2.29°$ (undiluted)

ee> 99% (determined by gas chromatography after derivatization with Mosher's reagent)

Example XXXVI

[R,R]-8-Benzyl-2,8-diazabicyclo[4.3.0]nonane



At 80°C, 75 g (0.5 mol) of L-(+)-tartaric acid are dissolved in 250 ml of dimethylformamide, and 54.1 g (0.25 mol) of cis-8-benzyl-2,8-diazabicyclo[4.3.0]nonane are added dropwise as a solution in 75 ml of dimethylformamide. The mixture is slowly cooled to 20°C, and the crystal suspension is stirred for another 1 hour. The crystals ([R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartrate) are filtered off with suction. (The filtrate can be processed further to give [S,S]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane). These crystals are washed with dimethylformamide and methoxyethanol (crude yield: 49.2 g) and recrystallized from 300 ml of methoxyethanol. This gives 45.6 g of enantiomerically pure [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane L-tartrate (enantiomeric purity determined by gas chromatography after derivatization with menthyl chloroformate).

Melting point: 121-124°C

$[\alpha]_D^{24} = +22.3°$ (c = 1, H_2O)

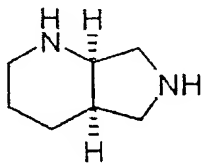
The resulting salt is now converted into the free base. To this end, 44.5 g are dissolved in 280 ml of water, and 35.6 g of 45% strength aqueous sodium hydroxide solution are added. The precipitated oil is taken up in 170 ml of tert-butyl methyl ether and the aqueous phase is re-extracted with 170 ml of tert-butyl methyl ether. The organic phases are combined and, after drying over sodium sulphate, concentrated. The residue is then distilled under reduced pressure.

Boiling point: 107-111°C/0.04 mbar

$[\alpha]_D^{24} = -17.5°$ (undiluted)

Example XXXVII

[R,R]-2,8-Diazabicyclo[4.3.0]nonane



19.4 g (0.09 mol) of [R,R]-8-benzyl-2,8-diazabicyclo[4.3.0]nonane in 130 ml of methanol are hydrogenated over 3.96 g of palladium on carbon (5%) at 90°C and

90 bar for 5 hours. The catalyst is then filtered off with suction and washed with methanol and the filtrate is concentrated under reduced pressure. The residue is distilled without fractionation.

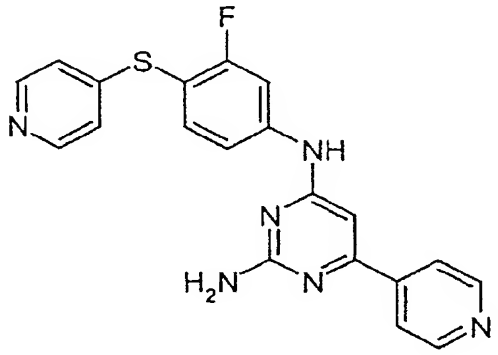
This gives 9.61 g (85% of theory) of product.

Boiling point: 45-58°C/0.08 mbar

$[\alpha]_D^{24} = +2.30°$ (undiluted)

Example XXXVIII

N-[2-Amino-6-(4-pyridinyl)-4-pyrimidinyl]-N-[3-fluoro-4-(4-pyridinylsulphanyl)-phenyl]amine



29.6 ml of water are added to 4.32 g (20.9 mmol) of Example V and 4.61 g (20.9 mmol) of Example XI. 9.25 ml of concentrated hydrochloric acid are added to the mixture, which is then stirred at 100°C overnight. After cooling to room temperature, the mixture is diluted with methanol and neutralized with saturated aqueous sodium bicarbonate solution. The mixture is absorbed on silica gel and purified by column chromatography on silica gel 60 using dichloromethane/methanol 95:5 → methanol.

Yield: 3.87 g (47% of theory)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.65 (s, 1H), 6.71 (s, 2H), 7.02 (dd, 2H), 7.47-7.58 (m, 2H), 7.87 (dd, 2H), 8.30-8.41 (m, 3H), 8.72 (d, 2H), 9.90 (s, 1H)

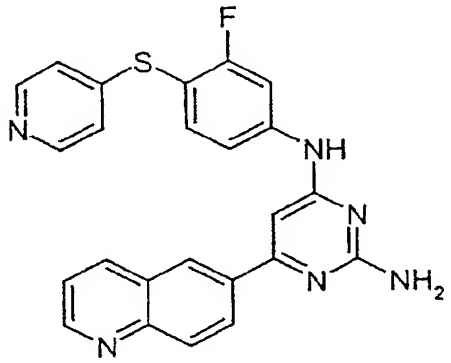
LC-MS (method 1): R_t = 3.34 min

MS (ESIpos): m/z = 391 $(M+H)^+$

Working Examples

Example 1

N-[2-Amino-6-(6-quinolinyl)-4-pyrimidinyl]-N-[3-fluoro-4-(4-pyridinylsulphanyl)-phenyl]amine



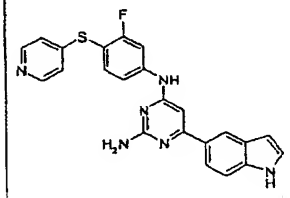
1.50 g (5.84 mmol) of the compound from Example II are, together with 1.29 g (5.84 mmol) of the compound from Example XI, initially charged in 70 ml of water, and 10 drops of concentrated hydrochloric acid (37% strength) are added. The suspension is stirred at 100°C overnight. After cooling, the reaction mixture is made alkaline using concentrated sodium bicarbonate solution and evaporated to dryness under reduced pressure.

The residue is purified by preparative HPLC and then by flash chromatography on silica gel using the mobile phase dichloromethane/methanol 30/1.

This gives 330 mg (12% of theory) of product.

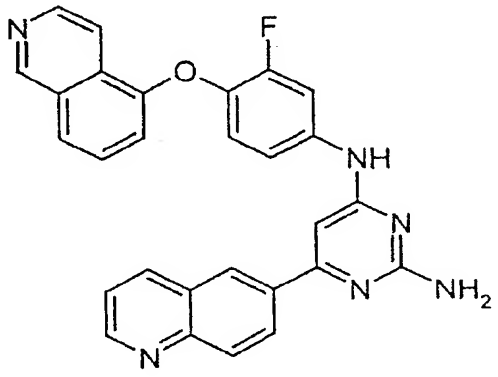
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.66 (br.s, 2H), 6.74 (s, 1H), 7.01 (d, 2H), 7.53 (d, 1H), 7.56-7.62 (m, 2H), 8.13 (d, 1H), 8.32-8.38 (m, 4H), 8.50 (d, 1H), 8.58 (d, 1H), 8.95 (dd, 1H), 9.87 (s, 1H)
HPLC (method 1): R_t = 4.22 min

The example listed in the table below can be prepared analogously to the procedure described for Example 1 from the appropriate starting materials.

Example	Structure	Analytical data
2		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.44 (br.s, 2H), 6.54 (br.s, 1H), 6.60 (s, 1H), 6.99 (d, 1H), 7.01 (s, 1H), 7.40 (d, 1H), 7.45-7.54 (m, 4H), 7.74 (d, 1H), 8.23 (s, 1H), 8.36 (d, 3H), 9.68 (s, 1H) HPLC (method 1): R_t = 3.80 min

Example 3

N-[2-Amino-6-(6-quinolinyl)-4-pyrimidinyl]-N-[3-fluoro-4-(5-isoquinolinyloxy)-phenyl]amine



110 mg (0.29 mmol) of the compound from Example XVII are suspended in 12 ml of a solvent mixture of toluene and ethanol in the ratio 2:1. 10 mg (0.01 mmol) of tetrakis(triphenylphosphine)palladium(0) are added, and the mixture is stirred at room temperature for 20 minutes. 60 mg (0.35 mmol) of 6-quinolineboronic acid and 1 ml of a 2M sodium carbonate solution are then added to the suspension, which is then stirred under reflux overnight. After cooling, the reaction mixture is concentrated under reduced pressure. The residue is purified chromatographically on silica gel 60 (mobile phase: dichloromethane/methanol 30:1 → 10:1).

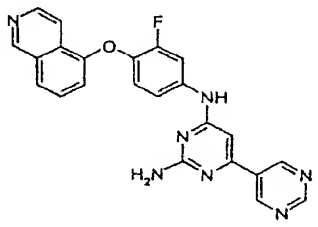
This gives 82 mg (60% of theory) of product.

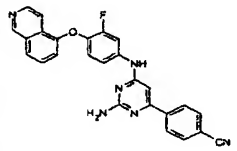
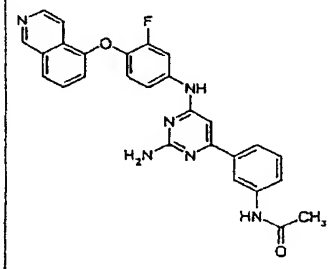
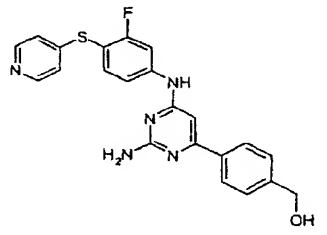
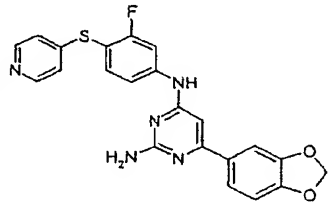
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.57 (br.s, 2H), 6.70 (s, 1H), 6.99 (d, 1H), 7.92 (t, 1H), 7.41-7.47 (m, 1H), 7.55-7.63 (m, 2H), 7.85 (d, 1H), 8.13 (t, 2H), 8.28-8.37 (m, 2H), 8.50 (br.d, 1H), 8.58-8.62 (m, 2H), 8.95 (dd, 1H), 9.39 (s, 1H), 9.66 (br.s, 1H)

HPLC (method 1): R_t = 3.49 min.

MS (ESIpos): m/z = 475 $(M+H)^+$

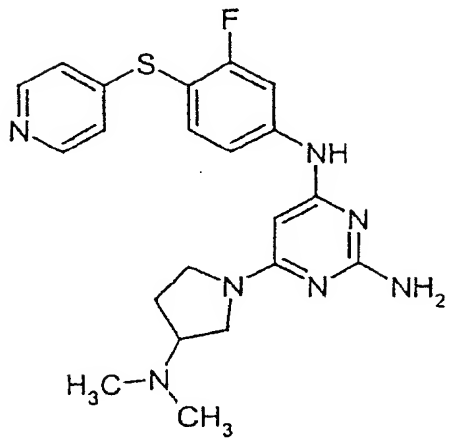
The examples listed in the table below can be prepared analogously to the procedure described for Example 3 from the appropriate starting materials.

Example	Structure	Analytical data
4		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.84 (s,1H), 7.01 (s, 1H), 7.18 (s, 1H), 7.30 (d, 1H), 7.41 (t,1H), 7.58 (br.d, 7.80 (t, 1H), 8.12 (d, 1H), 8.29 (d, 1H), 8.44 (d, 1H), 8.70 (d, 1H) 9.30 (s, 2H), 9.41 (s, 1H), 9.75 (s, 1H), 11.25 (br.s, 1H) LC-MS (method 5): R_t = 2.42 min MS (ESIpos): m/z = 426 $(M+H)^+$

Example	Structure	Analytical data
5		LC-MS (method 5): R_t = 2.73 min MS (ESIpos): m/z = 449 $(M+H)^+$
6		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 6.68 (s, 1H), 7.25 (d, 1H), 7.40 (t, 1H), 7.53-7.66 (m, 4H), 7.67-7.76 (m, 1H), 7.76 (t, 1H), 8.08 (d, 1H), 8.28-8.39 (m, 4H), 8.68 (d, 1H), 9.68 (s, 1H), 10.34 (s, 1H), 11.21 (s, 1H) LC-MS (method 5): R_t = 2.53 min MS (ESIpos): m/z = 481 $(M+H)^+$
7		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 4.62 (s, 2H), 6.86 (s, 1H), 7.46 (d, 2H), 7.58 (d, 2H), 7.69-7.77 (m, 2H), 7.88 (d, 2H), 8.41 (br.d, 1H), 8.56 (d, 2H), 11.51 (s, 1H) LC-MS (method 3): R_t = 1.84 min MS (ESIpos): m/z = 420 $(M+H)^+$
8		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.07 (br.s, 2H), 3.13 (s, 3H), 3.20 (br.s, 2H), 3.52 (br.s, 2H), 4.63 (br.s, 1H), 5.17 (s, 1H), 6.03 (br.s, 2H), 6.97 (d, 2H), 7.33-7.49 (m, 2H), 8.25 (dd, 1H), 8.34 (d, 2H), 9.29 (s, 1H) LC-MS (method 3): R_t = 2.33 min MS (ESIpos): m/z = 434 $(M+H)^+$

Example 9

N-{2-Amino-6-[3-(dimethylamino)-1-pyrrolidinyl]-4-pyrimidinyl}-N-[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]amine



600 mg (1.73 mmol) of the compound from Example XVI are dissolved in 40 ml of ethanol, and 788 mg (6.9 mmol) of 3-(dimethylamino)pyrrolidine and 3 ml (17.25 mmol) of N,N-diisopropylethylamine are added. The mixture is stirred at 80°C overnight. After cooling, the reaction solution is purified by MPLC (mobile phase: dichloromethane/methanol 5:1 + 1% concentrated ammonia solution).

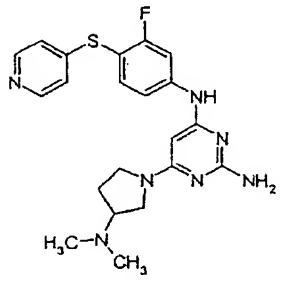
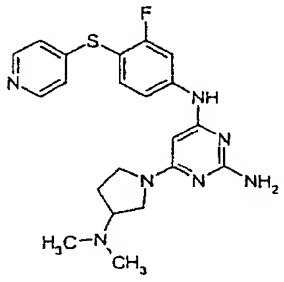
This gives 475 mg (58% of theory) of product. (Mixture of enantiomers)

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.69-1.83 (m, 1H), 2.06-2.15 (m, 1H), 2.20 (s, 6H), 2.69-2.80 (m, 1H), 3.05 (t, 1H), 3.43-3.70 (br.m, 2H), 4.05 (q, 1H), 5.16 (s, 1H), 5.95 (br.s, 2H), 6.97 (d, 2H), 7.36-7.47 (m, 2H), 8.21 (dd, 1H), 8.34 (dd, 2H), 9.23 (s, 1H)

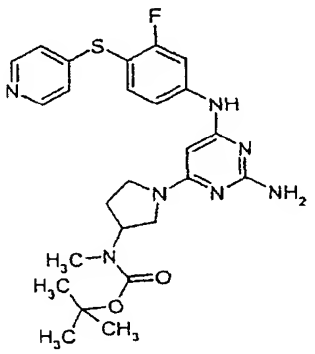
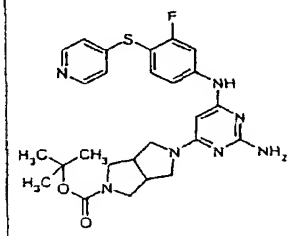
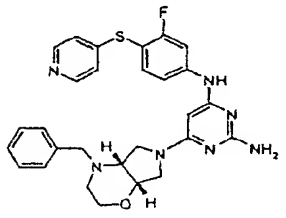
LC-MS (method 7): R_t = 0.44 min

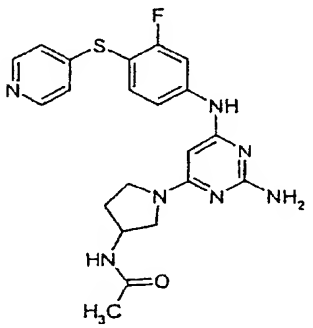
MS (ESIpos): m/z = 426 $(M+H)^+$

The two enantiomers below are obtained form Example 9 by separating the enantiomers using chiral HPLC (Method 11).

Example	Structure	Analytical data
10	 (-)-enantiomer	Chiral HPLC (method 11): R_t = 6.79 min
11	 (+)-enantiomer	Chiral HPLC (method 11): R_t = 5.77 min

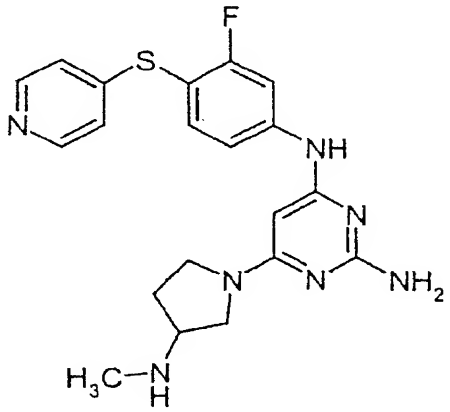
The examples listed in the table below can be prepared analogously to the procedure described for Example 9 from the corresponding starting materials.

Example	Structure	Analytical data
12		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.42 (s, 9H), 2.07 (m, 2H), 2.74 (s, 3H), 3.20 (m, 2H), 3.52 (m, 2H), 4.63 (q, 1H), 5.17 (s, 1H), 6.03 (br.s, 2H), 6.97 (d, 2H), 7.33-7.49 (m, 2H), 8.25 (dd, 1H), 8.34 (d, 2H), 9.29 (s, 1H) LC-MS (method 6): R_t = 1.79 min MS (ESIpos): m/z = 512 $(M+H)^+$
13		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.39 (s, 9H), 2.92 (m, 2H), 3.16 (m, 4H), 3.52 (m, 4H), 5.16 (s, 1H), 5.95 (br.s, 2H), 6.97 (d, 2H), 7.36-7.47 (m, 2H), 8.20 (dd, 1H), 8.34 (d, 2H), 9.25 (s, 1H) LC-MS (method 7): R_t = 3.04 min MS (ESIpos): m/z = 524 $(M+H)^+$
14	 Chiral	^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.57-1.83 (m, 1H), 2.43-2.56 (m, 1H), 2.68-2.99 (m, 1H), 3.30-3.52 (m, 3H), 3.57-3.98 (m, 6H), 4.14 (br.s, 1H), 4.66 (br.s,1H), 5.12 (br.s, 1H), 5.30 (s, 1H), 6.52 (s, 1H), 6.94 (d, 1H), 7.07 (dd, 1H), 7.28-7.48 (m, 6H), 7.60 (dd, 1H), 8.35 (d, 2H) LC-MS (method 7): R_t = 2.90 min MS (ESIpos): m/z = 530 $(M+H)^+$

Example	Structure	Analytical data
15		^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.70-1.90 (m, 1H), 1.78 (s, 3H), 2.68-3.01 (m, 1H), 3.16-3.61 (m, overlaps with H_2O signal, ~ 3H)), 4.18-4.32 (m, 1H), 5.15 (s, 1H), 5.98-6.10 (br.s., 2H), 6.98 (d, 2H), 7.31-7.49 (m, 2H), 8.14 (d, 1H), 8.28 (dd, 1H), 8.38 (dd, 2H), 9.29 (s, 1H) LC-MS (method 7): R_t = 2.58 min MS (ESIpos): m/z = 440 $(M+H)^+$

Example 16

N-[1-(2-Amino-6-{[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]amino}-4-pyrimidinyl)-3-pyrrolidinyl]-N-methylamine



8 ml of 4M hydrochloric acid in dioxane are added to 46 mg (0.09 mmol) of the compound from Example 12, and the mixture is stirred at room temperature for 4 hours. The mixture is then concentrated under reduced pressure. A little concentrated ammonia solution is added to the residue, the mixture is concentrated

using a rotary evaporator and the residue is then suspended in 2 ml of water. The precipitate is filtered off with suction and washed with 2 ml of dichloromethane.

This gives 23 mg (62% of theory) of product.

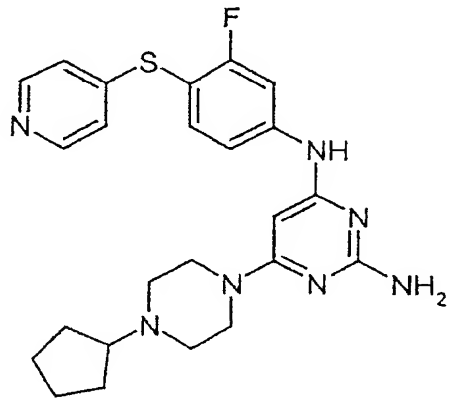
^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.40 (s, 3H), 2.60 (s, 1H), 3.51-3.90 (m, 6H), 5.29 (s, 1H), 7.00 (d, 1H), 7.16 (s, 1H), 7.33-7.52 (m, 3H), 8.18 (br.d, 1H), 8.36 (d, 1H)

LC-MS (method 1): R_t = 0.68 min

MS (ESIpos): m/z = 412 $(M+H)^+$

Example 17

N-[2-Amino-6-(4-cyclopentyl-1-piperazinyl)-4-pyrimidinyl]-N-[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]amine



300 mg (0.86 mmol) of the compound from Example XVI are suspended in 8 ml of 2-ethyl-1-hexanol, and 266 mg (1.73 mmol) of 1-cyclopentylpiperazine and 0.75 ml (4.31 mmol) of N,N-diisopropylethylamine are added. The mixture is stirred at 150°C overnight. After cooling, the reaction solution is purified by MPLC (mobile phase: dichloromethane/methanol 10:1 + 1% concentrated ammonia solution).

216 mg (52% of theory) of product are obtained.

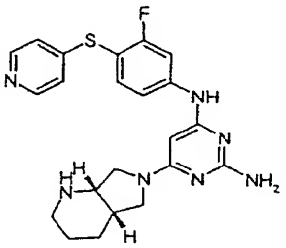
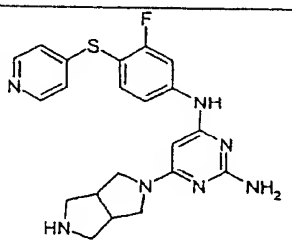
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.28-1.41 (m, 2H), 1.44-1.55 (m, 2H), 1.57-1.68 (m, 2H), 1.70-1.85 (m, 2H), 2.43 (br.s, 5H), 3.41 (br.s, 4H), 5.39 (s, 1H), 6.04

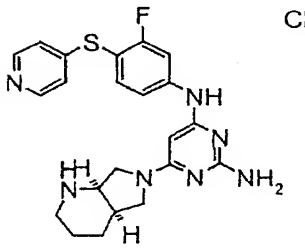
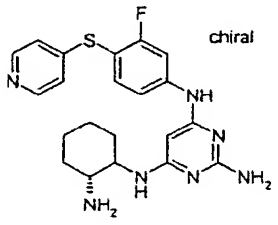
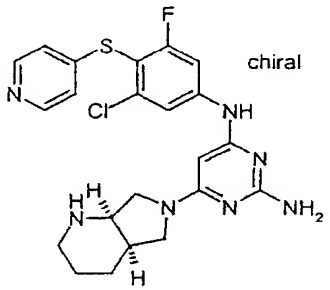
(br.s, 2H), 6.97 (d, 2H), 7.36 (dd, 1H), 7.45 (t, 1H), 8.23 (dd, 1H), 8.34 (d, 2H), 9.28 (s, 1H)

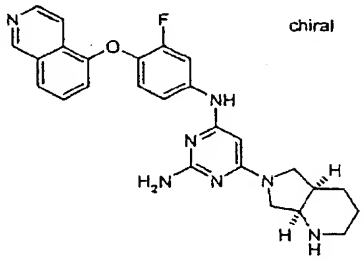
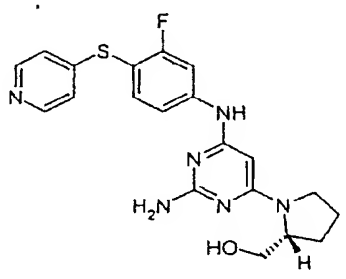
LC-MS (method 7): R_t = 2.38 min

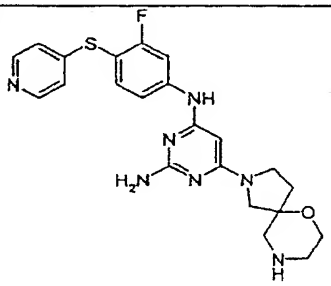
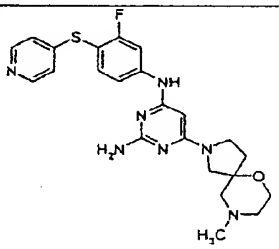
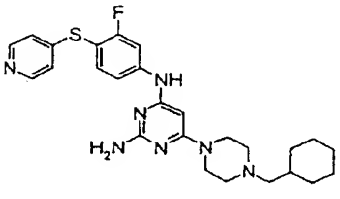
MS (ESIpos): m/z = 466 $(M+H)^+$

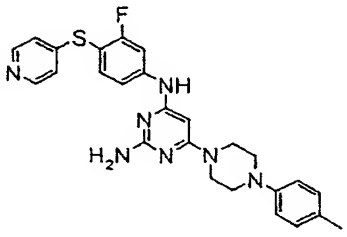
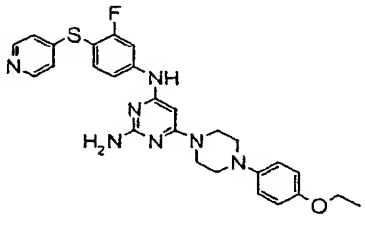
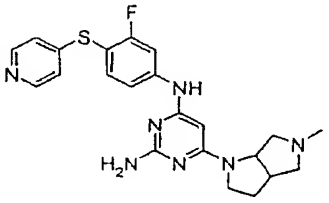
The examples in the table below can be prepared analogously to the procedure described for Example 17 from the corresponding starting materials.

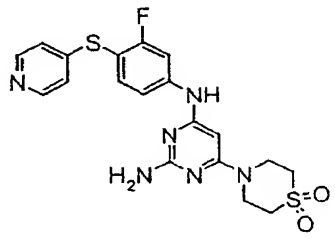
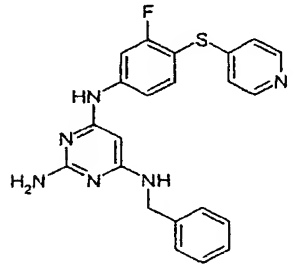
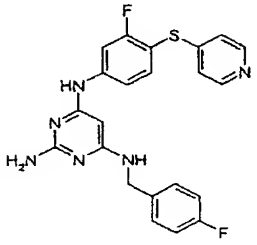
Example	Structure	Analytical data
18	 Chiral	^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.21-1.74 (m, 5H), 2.09-2.33 (m, 1H), 2.72-2.93 (m, 2H), 3.06-3.26 (m, 3H), 3.42-3.65 (m, 1H), 5.12 (s, 1H), 5.76 (s, 1H), 5.95 (br.s, 1H), 6.98 (d, 2H), 7.33-7.49 (m, 2H), 8.24 (dd, 1H), 8.34 (d, 2H), 9.25 (s, 1H) LC-MS (method 6): R_t = 0.34 min MS (ESIpos): m/z = 438 $(M+H)^+$
19		LC-MS (method 7): R_t = 0.41 min MS (EIneg): m/z = 422 (M-)

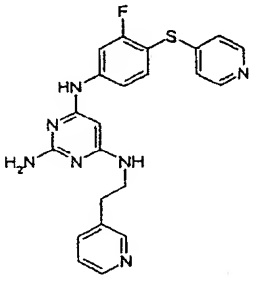
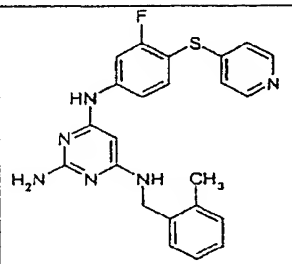
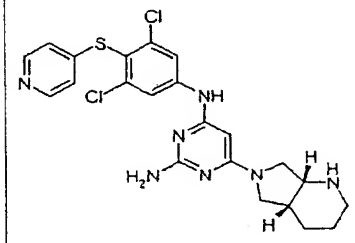
Example	Structure	Analytical data
20	 Chiral	^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.23-1.75 (m, 5H), 2.21 (br.s, 2H), 2.84 (d, 1H), 3.63-3.22 (m, 4H), 4.11 (q, 1H), 5.11 (s, 1H), 5.94 (br.s, 2H), 6.97 (d, 2H), 7.32-7.49 (m, 2H), 8.29 (dd, 1H), 8.34 (d, 2H), 9.23 (s, 1H) LC-MS (method 7): R_t = 0.37 min MS (ESIpos): m/z = 438 $(M+H)^+$
21	 chiral	^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.03- 1.22 (m, 4H), 1.23 (s, 2H), 1.65 (br.s, 2H), 1.87 (t, 2H), 3.16 (s, 2H), 5.26 (s, 1H), 5.86 (s, 2H), 6.35 (d, 1H), 6.97 (d, 2H), 7.36 (d, 1H), 7.43 (t, 1H), 8.17 (d, 1H), 8.35 (d, 2H), 9.15 (s, 1H) MS (ESIpos): m/z = 426 $(M+H)^+$ LC/MS (method 1): R_t = 3.53 min
22	 chiral	^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.36- 1.47 (m, 1H), 1.52- 1.75 (m, 3H), 2.22- 2.38 (m, 1H), 2.57 (t, 1H), 2.84- 2.93 (m, 1H), 3.17 (s, 3H), 4.06 (br.s, 1H), 5.14 (s, 1H), 6.00 (s, 2H), 6.97 (d, 2H), 7.74 (s, 1H), 8.12 (dd, 1H), 8.36 (d, 2H), 9.42 (s, 1H) MS (ESIpos): m/z = 472 $(M+H)^+$ LC/MS (method 1): R_t = 3.53 min

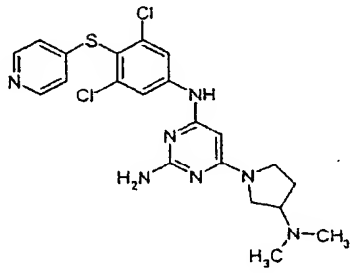
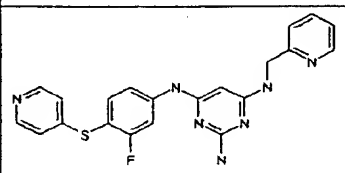
Example	Structure	Analytical data
23		^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.34-1.66 (m, 5H), 2.04-2.29 (m, 2H), 2.80-2.83 (m, 1H), 3.17 (d, 3H), 4.09 (q, 1H), 5.07 (s, 1H), 5.75 (s, 1H), 5.82 (s, 2H), 6.93 (d, 1H), 7.19 (br.d, 1H), 7.56 (t, 1H), 7.82 (d, 1H), 8.10 (d, 1H), 8.17 (dd, 1H), 8.59 (d, 1H), 8.92 (s, 1H), 9.36 (s, 1H) MS (ESIpos): m/z = 472 $(M+H)^+$
24		^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.82- 2.10 (m,5H), 3.29-3.30 (m, 4H), 3.41-3.48 (m, 1H), 3.54- 3.65 (m, 2H), 4.15 (br.s, 1H), 5.29 (s, 1H), 7.02 (d, 2H), 7.34 (dd, 1H), 7.42 (t, 1H), 7.93 (dd, 1H), 8.25 (d, 2H) MS (ESIpos): m/z = 413 $(M+H)^+$ HPLC (method 1): R_t = 3.48 min

Example	Structure	Analytical data
25	 from Example XVI and Example XXIV; during the chromatographic purification with addition of acid, the Boc group is cleaved off	MS (CIpos): m/z = 454 $(M+H)^+$ HPLC (method 1): R_t = 3.39 min
26		MS (ESIpos): m/z = 468 $(M+H)^+$ HPLC (method 1): R_t = 3.41 min
27		^{1}H-NMR (300 MHz, DMSO-d_6):δ =0.92- 1.03 (m, 2H), 1.13- 1.30 (m, 5H), 1.64- 1.80 (m, 6H), 2.99 (d, 6H), 4.22 (d, 2H), 5.53 (s, 1H), 6.42 (br.s, 1H), 7.22 (d, 2H), 7.40 (dd, 1H), 7.52 (t, 1H), 8.19 (d, 1H9, 8.45 (d, 1H), 9.31 (br.s, 1H), 9.57 (s, 1H) MS (ESIpos): m/z = 494 $(M+H)^+$ HPLC (method 1): R_t = 3.77 min

Example	Structure	Analytical data
28		^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.50 (s, 3H), 3.20 (br.s, 4H), 3.64 (br.s, 4H), 5.61 (s, 1H), 6.89 (d, 3H), 7.06 (d, 3H), 7.19 (d, d, 2H), 7.38 (dd, 1H), 7.58 (t, 1H), 8.07 (br.s, 1H), 8.44 (d, 2H), 9.85 (br.s, 1H) MS (ESIpos): m/z = 488 $(M+H)^+$ HPLC (method 1): R_t = 3.81 min
29		^{1}H-NMR (400MHz, MeOH-d_4): δ = 1.35 (t, 3H), 3.19 (t, 4H), 3.75 (s, 4H), 3.98 (quart., 2H), 4.89 (s,1H), 6.85 (d, 2H), 6.99 (d, 2H), 7.43 (d, 3H), 7.65 (t, 1H), 7.84 (br.s, 1H), 8.43 (d, 2H) MS (ESIpos): m/z = 518 $(M+H)^+$ HPLC (method 1): R_t = 3.82 min
30		^{1}H-NMR (400 MHz, MeOH-d_4): δ = 1.29-1.41 (m, 2H), 2.03 (br.s, 1H), 2.32 (br.s, 1H), 2.67 (s, 2H), 2.95 (s, 5H), 3.61-3.68 (m, 2H), 4.67 (s, 1H), 7.14 (d, 3H), 7.38 (dd, 1H), 7.52 (t, 2H), 7.93 (d, 1H), 8.32 (dd, 3H) HPLC (method 1): R_t = 3.35 min

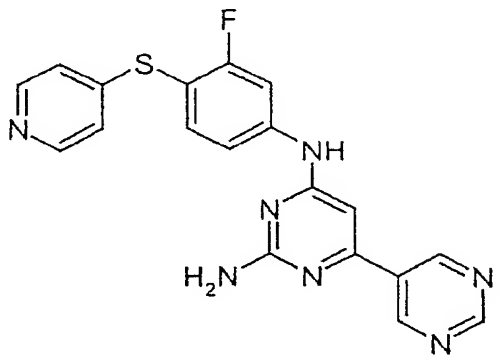
Example	Structure	Analytical data
31		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 3.17 (br.s, 4H), 3.97 (br.s, 4H), 5.61 (s, 1H), 7.29 (d, 3H), 7.39 (dd, 1H), 7.54 (t, 1H), 8.15 (br.d, 1H), 8.48 (d, 3H), 9.61 (br.s, 1H) MS (ESIpos): m/z = 447 $(M+H)^+$ HPLC (method 1): R_t = 3.38 min
32		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 4.47 (d, 3H), 5.41 (s, 1H), 7.21 (d, 3H), 7.32 (d, 4H), 7.43- 7.48 (m, 1H), 7.61 (t, 1H), 7.64- 7.86 (m, 1H), 8.00- 8.16 (m, 1H), 8.24-8.33 (m, 1H), 8.46 (d, 2H), 10.17 (s, 1H) MS (ESIpos): m/z = 419 $(M+H)^+$ HPLC (method 1): R_t = 3.85 min
33		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 4.43- 4.50 (m, 3H), 5.39 (s, 1H), 7.15- 7.29 (m, 5H9, 7.32- 7.44 (m, 4H), 7.52-7.66 (m, 2H), 8.44 (dd, 2H), 10.14 (br.s, 1H) MS (ESIpos): m/z = 437 $(M+H)^+$ HPLC (method 1): R_t = 3.89 min

Example	Structure	Analytical data
34		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.22 (d, 1H), 1.26 (d, 1H), 3.52 (d, H), 5.51 (s, 1H), 7.38 (d, 3H), 7.64 (t,2H), 7.72-7.78 (m, 2H), 8.19 (d, 2H), 8.53 (d, 2H), 8.66- 8.73 (m, 3H), 10.26 (s, 1H) MS (ESIpos): m/z = 434 $(M+H)^+$ HPLC (method 1): R_t = 3.34 min
35		MS (ESIpos): m/z = 433 $(M+H)^+$ LC/MS (method 4): R_t = 2.90 min
36		^{1}H-NMR (200 MHz, DMSO-d_6): δ = 1.04-1.10 (m, 1H), 1.44-1.66 (m, 6H), 2.47-2.62 (m, 1H), 2.69-2.84 (m, 2H), 2.96-3.13 (m, 4H), 5.06 (s, 1H), 6.88 (d, 2H), 7.91 (s, 2H), 8.23 (d, 2H), 8.83 (br.s, 1H), 9.55 (br.s, 1H) MS (ESIpos): m/z = 488 $(M+H)^+$ HPLC (method 1): R_t = 3.61 min

Example	Structure	Analytical data
37		^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.22-1.28 (m, 1H), 2.15-2.26 (m, 1H), 2.84 (s, 6H), 3.17 (s, 1H), 3.82 (m, 3H), 3.92-4.02 (m, 2H) 5.26 (s, 1H), 7.07 (d, 2H9, 8.09 (s, 2H), 8.42 (d, 2H), 9.71 (br.s, 1H), 10.05 (br.s, 1H) HPLC (method 1): R_t = 3.57 min
38		MS (ESIpos): m/z = 419 $(M+H)^+$ LC-MS (method 4): R_t = 2.30 min

Example 39

N-(2-Amino-4,5'-bipyrimidin-6-yl)-N-[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]-amine



100 mg (0.253 mmol) of the compound from Example XI are initially charged in 10 ml of dimethylformamide, and 350 mg (2.53 mmol) of potassium carbonate are added. In an argon countercurrent, 52.13 mg (2.53 mmol) of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine and 20.7 mg (0.025 mmol) of 1,1'-bis(diphenyl-phosphine)ferrocene-dichloropalladium(II) complex are added with dichloro-methane. After a short period of time, the colour of the reaction solution turns to

black. The mixture is stirred at 120°C overnight. After cooling, the reaction mixture is diluted with about 30 ml of ethyl acetate and extracted with water. The aqueous phase is re-extracted twice with 20 ml of ethyl acetate. The organic phase is washed once with saturated sodium chloride solution, dried over sodium sulphate and concentrated under reduced pressure. The dark-brown residue is purified on silica gel 60 (mobile phase: dichloromethane/methanol 20:1). Since it was not possible to isolate a clean product, the product was purified once more by preparative HPLC.

This gives 9 mg (8% of theory) of product.

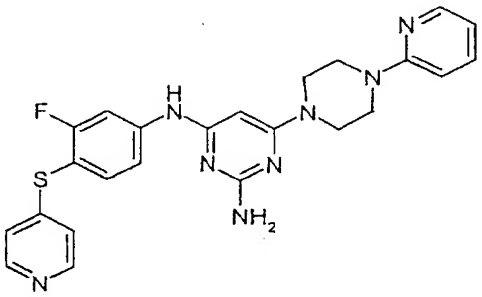
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 6.66 (s, 1H), 7.33 (d, 2H), 7.55-7.65 (m, 2H), 8.40 (dd, 1H), 8.50 (br.s, 2H), 9.25 (s, 2H), 9.32 (s, 1H), 10.26 (br.s 1H).

MS (ESIpos): m/z = 392 $(M+H)^+$

HPLC (method 1): R_t = 3.53 min

Example 40

N-{2-Amino-6-[4-(2-pyridinyl)-1-piperazinyl]-4-pyrimidinyl}-N-[3-fluoro-4-(4-pyridinylsulphanyl)phenyl]amine



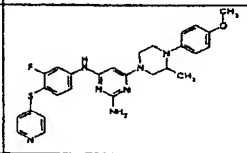
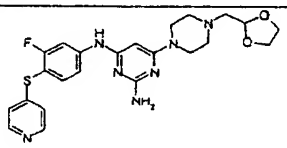
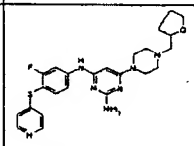
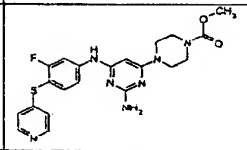
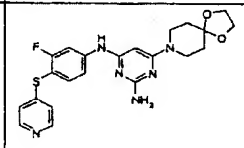
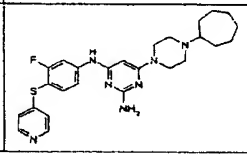
34.78 mg (0.1 mmol) of the compound from Example XVI are dissolved in 0.5 ml of dimethylformamide, and 32.6 mg (0.2 mmol) of 1-(2-pyridinyl)piperazine and 25.8 mg (0.2 mmol) of N,N-diisopropylethylamine are added. The mixture is stirred at 120°C overnight. For work-up, the reaction solution is purified initially by LC-MS and then once more by UV/HPLC.

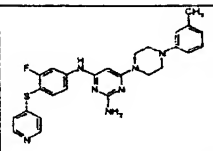
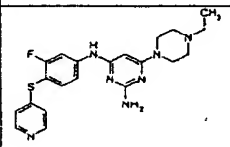
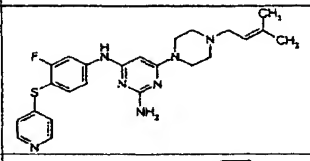
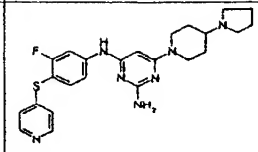
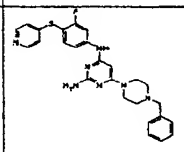
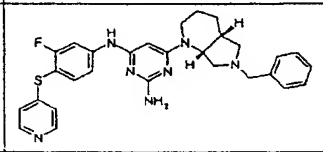
13.1 mg (20% of theory) of product are obtained.

LC-MS (method 4): R_t = 1.30 min

MS (ESIpos): m/z = 475 $(M+H)^+$

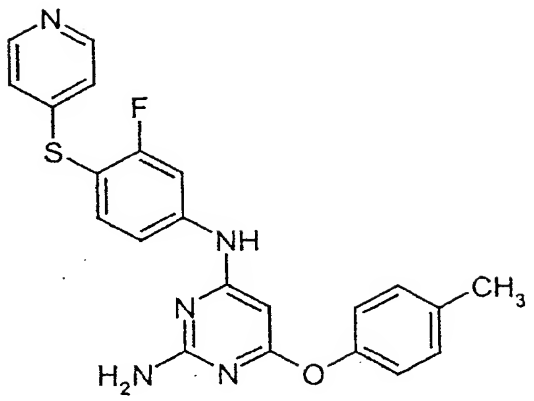
The examples listed in the table below can be prepared analogously to the procedure described for Example 40 using Example XVI and the appropriate starting materials.

Example	Structure	Analytical data
41		LC-MS (method 4): R_t = 2.80 min MS (ESIpos): m/z = 518 $(M+H)^+$
42		LC-MS (method 4): R_t = 0.70 min MS (ESIpos): m/z = 484 $(M+H)^+$
43		LC-MS (method 4): R_t = 0.70 min MS (ESIpos): m/z = 482 $(M+H)^+$
44		LC-MS (method 4): R_t = 2.40 min MS (ESIpos): m/z = 456 $(M+H)^+$
45		LC-MS (method 4): R_t = 2.40 min MS (ESIpos): m/z = 455 $(M+H)^+$
46		LC-MS (method 4): R_t = 2.20 min MS (ESIpos): m/z = 494 $(M+H)^+$

Example	Structure	Analytical data
47		LC-MS (method 4): R_t = 3.10 min MS (ESIpos): m/z = 4.88 $(M+H)^+$
48		LC-MS (method 4): R_t = 0.50 min MS (ESIpos): m/z = 426 $(M+H)^+$
49		LC-MS (method 4): R_t = 1.30 min MS (ESIpos): m/z = 466 $(M+H)^+$
50		LC-MS (method 4): R_t = 0.50 min MS (ESIpos): m/z = 466 $(M+H)^+$
51		LC-MS (method 4): R_t = 1.90 min MS (ESIpos): m/z = 488 $(M+H)^+$
52		LC-MS (method 4): R_t = 2.30 min MS (ESIpos): m/z = 528 $(M+H)^+$

Example 53

N-[2-Amino-6-(4-methoxyphenoxy)-4-pyrimidinyl]-N-[3-fluoro-4-(4-pyridinyl-sulphanyl)phenyl]amine



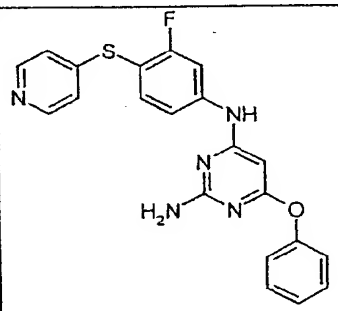
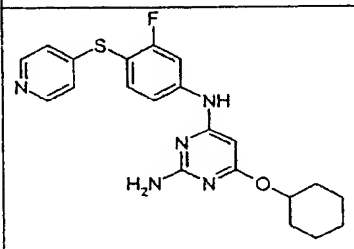
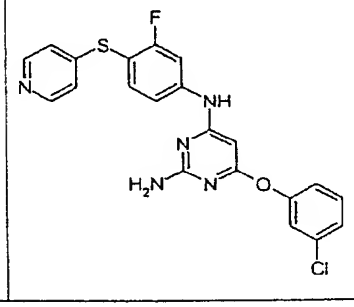
30 mg (0.086 mmol) of the compound from Example XVI, 37.31 mg (0.345 mmol) of p-cresol and 9.679 mg (0.173 mmol) of solid potassium hydroxide are mixed thoroughly and, as a melt, stirred under argon at 150°C for 3 hours. For work-up, the melt is purified by column chromatography on silica gel 60 using dichloromethane/methanol 95:5.

This gives 15 mg (41% of theory) of product.

LC-MS (method): R_t = 2.40 min

MS (ESIpos): m/z 420 $(M+H)^+$

The examples listed in the table below can be prepared analogously to the procedure described for Example 53 from the appropriate starting materials.

Example	Structure	Analytical data
54		LC-MS (method 10): R_t = 2.20 min MS (ESIpos): m/z = 406 $(M+H)^+$
55		LC/MS (method 10): R_t = 2.27 min MS(ESIpos): m/z = 412 $(M+H)^+$
56		LC/MS (method 10): R_t =2.56 min MS(ESIpos): m/z = 440 $(M+H)^+$

B. Assessment of the physiological activity

The inhibition of the enzyme is investigated in an in vitro assay with recombinant Rho kinase II. The vessel-relaxing action is determined using phenylephrin-induced contractions of isolated rings of the saphenous artery of rabbits. The suitability of the compounds according to the invention for treating cardiovascular disorders can be demonstrated by examining the hypotensive effect on anaesthetized rats.

Inhibition of recombinant Rho kinase II (ROKα)

The activity of Rho kinase is determined by the uptake of ^{33}P phosphate into a substrate peptide. To this end, commercially available Rho kinase II (Upstate Biotechnology) is pre-incubated at 37°C in the presence of the S6 phosphate-acceptor peptide with the test substances or a solvent control for 10 min. The kinase reaction is then started by addition of ^{33}P-labelled ATP. After 20 min at 37°C, the reaction is stopped by addition of H_3PO_4. Aliquots are pipetted onto filters and the filters are washed and then covered with scintillator. The radioactivity of the ^{33}P-labelled peptides bound to the filter is measured in a Micro-Beta* counter. The IC_{50} value corresponds to the concentration of a test substance at which the Rho-kinase-catalysed uptake of ^{33}P into the peptide is inhibited by 50%, compared to a solvent control. The experimental data are summarized in the table below.

Example No.	IC_{50} (nM)
1	7
20	11
21	25
22	6
56	70

Vessel-relaxing action in vitro

Individual 3-mm-wide rings of the isolated saphenous artery of rabbits are introduced into 5 ml organ baths with Krebs-Henseleit solution (37°C, gassed with carbogen). The vessel tone is monitored isometrically and registered. Contractions are induced by addition of 3×10^{-8} g of phenylephrin/ml, which is washed out again after 4 min. After a number of control cycles, the rings are pre-incubated with the substance to be examined, with the dosage being increased for each further cycle, and the subsequent contraction is compared to the intensity of the last control contraction. The concentration required to reduce the intensity of the control value by 50% (IC_{50}) is calculated. The experimental data are summarized in the table below.

*Trade-mark

Example No.	IC_{50} (nM)
1	760
20	1700
21	870
22	900

Measurement of blood pressure in anaesthetized rats

Male Wistar rats of a body weight of 300 - 350 g are anaesthetized with thiopental (100 mg/kg i.p.). Following tracheotomy, a catheter is introduced into the femoral artery to measure the blood pressure. The substances to be tested are administered as solutions, either orally via a stomach tube or intravenously via the femoral vein.

C. Working examples for pharmaceutical compositions

The compounds according to the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound from Example 1, 50 mg of lactose (monohydrate), 50 mg of maize starch (native), 10 mg of polyvinylpyrrolidone (PVP 25) (from BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, spherical radius 12 mm.

Preparation:

The mixture of active compound, lactose and starch is granulated with a 5% strength solution (w/w) of the PVP in water. After drying, the granules are mixed for 5 min with the magnesium stearate. This mixture is compacted in a conventional tablet press (dimensions of the tablet: see above). The standard value used for compacting is a compaction force of 15 kN.

Suspension for oral administration:

Composition:

1000 mg of the compound from Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel* (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

A single dose of 100 mg of the compound according to the invention corresponds to 10 ml of oral suspension.

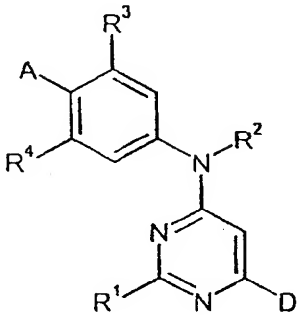
Preparation:

The Rhodigel is suspended in ethanol and the active compound is added to the suspension. The water is added with stirring. The mixture is stirred for about 6 h until the Rhodigel is completely swollen.

*Trade-mark

CLAIMS:

1. A compound of the formula



(I),

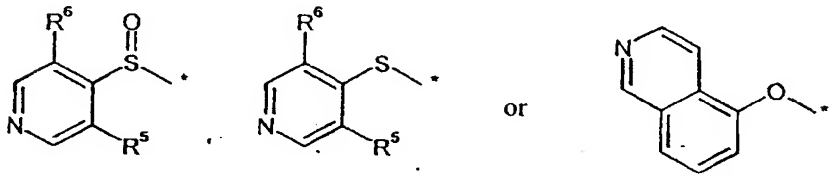
in which

R^1 represents amino or hydroxyl,

R^2 represents hydrogen, (C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl,

R^3 and R^4 independently of one another represent cyano, hydrogen, fluorine or chlorine,

A represents a radical



in which

R^5 and R^6 independently of one another represent hydrogen, fluorine or chlorine,

D (1) represents a radical selected from the group consisting of

phenyl, which for its part is substituted by (C_1-C_4)-alkylcarbonylamino, hydroxymethyl, cyano, (C_1-C_4)-alkoxymethyl or 1,2-dioxymethylene,

quinoline, isoquinoline, indole or 6-membered heteroaryl having 2 or 3 nitrogen atoms, where the rings are in each case attached via a carbon atom,

pyridylmethyl, 2-oxo-2H-pyridin-1-yl, 4-oxo-4H-pyridin-1-yl, which for their part may be substituted by fluorine, chlorine or (C_1-C_4)-alkyl, and

pyridyl, which for its part is substituted by fluorine, chlorine or (C_1-C_4)-alkyl,

or

(2) represents a radical *-OR^7,

in which

R^7 represents phenyl which may be substituted by trifluoromethyl, trifluoromethoxy, nitro, cyano, *-NR^8R^9, fluorine, chlorine or 1,2-dioxymethylene or by (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy, which for their part may be substituted by hydroxyl and/or *-NR^8R^9,

3- to 7-membered heterocyclyl having a nitrogen atom which may be substituted by hydrogen, (C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl,

5- or 6-membered heteroaryl having up to three nitrogen atoms,

(C_1-C_6)-alkyl or (C_3-C_7)-cycloalkyl which for their part may be substituted by hydroxyl or *-NR^8R^9,

thienyl, furyl, pyridylmethyl, naphthyl or benzyl,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl which for its part may be substituted by hydroxyl or amino, or

R^8 and R^9 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocycle which may have an additional oxygen atom or a group N-H or N-(C_1-C_4)-alkyl in the ring,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical *-$(CH_2)_x$-phenyl, where phenyl may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl, or represents *-$(CH_2)_y$-E,

in which

x represents 1, 2 or 3,

y represents 0, 1, 2 or 3 and

E represents pyrrolidine or piperidine, which for their part may be substituted by (C_1-C_4)-alkyl, or represents pyridyl which may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle which is substituted by *-$NR^{12}R^{13}$, 1,1-dioxyethylene, (C_1-C_4)-alkoxy, hydroxyl- or (C_1-C_4)-alkoxy-substituted (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl or 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

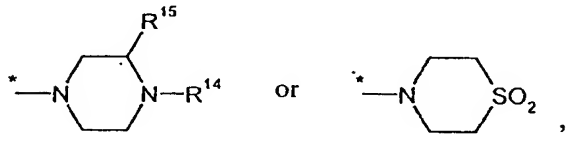
R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 7- to 12-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O in the ring and which may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl or benzyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a radical



in which

R^{14} represents (C_2-C_6)-alkenyl, (C_1-C_4)-alkoxycarbonyl or *-$(CH_2)_z$-G,

in which

z represents 0 or 1 and

G represents (C_3-C_8)-cycloalkyl, pyridyl, optionally (C_1-C_4)-alkyl- or (C_1-C_4)-alkoxy-substituted phenyl, tetrahydrofuran or 1,3-dioxolane,

and

R^{15} represents hydrogen or (C_1-C_4)-alkyl,

or a salt, hydrate, hydrate of the salt or solvate thereof.

2. A compound of the formula (I) according to claim 1,

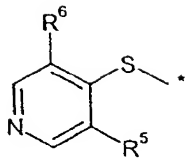
in which

R^1 represents amino,

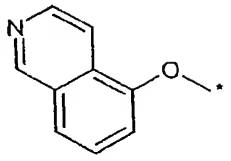
R^2 represents hydrogen,

R^3 and R^4 independently of one another represent hydrogen, fluorine or chlorine,

A represents a radical



or



,

in which

R^5 and R^6 represent hydrogen,

D (1) represents a radical selected from the group consisting of

phenyl which is substituted by (C_1-C_4)-alkylcarbonylamino, hydroxymethyl, (C_1-C_4)-alkoxymethyl or 1,2-dioxymethylene,

quinoline, indole or 6-membered heteroaryl having 2 or 3 nitrogen atoms, where the rings are in each case attached via a carbon atom,

pyridylmethyl, which may be substituted by (C_1-C_4)-alkyl,

and

pyridyl, which is substituted by (C_1-C_4)-alkyl,

or

(2) represents a radical *-OR^7,

in which

R^7 represents phenyl, which may be substituted by fluorine, chlorine, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy or 1,2-dioxymethylene,

(C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl, which for their part may be substituted by hydroxyl or *-NR^8R^9,

naphthyl or benzyl,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl or

R^8 and R^9 together with the nitrogen atom to which they are attached form a 5- to 7-membered heterocycle which may have an additional oxygen atom or a group N-H or N-(C_1-C_4)-alkyl in the ring,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical *-$(CH_2)_x$-phenyl, where phenyl may be substituted up to four times independently of one

another by fluorine, chlorine or (C_1-C_4)-alkyl, or represents *-$(CH_2)_y$-E,

in which

x represents 1 or 2,

y represents 0, 1 or 2 and

E represents pyrrolidine or piperidine, which for their part may be substituted by (C_1-C_4)-alkyl, or represents pyridyl which may be substituted up to four times independently of one another by fluorine, chlorine or (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle which is substituted by *-$NR^{12}R^{13}$, 1,1-dioxymethylene, (C_1-C_4)-alkoxymethyl or by 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)alkyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

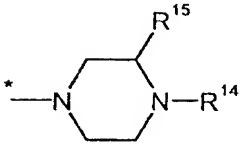
R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form an 8- to 10-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O in the ring and which may be substituted by (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl or benzyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a radical



in which

R^{14} represents (C_3-C_8)-cycloalkyl, (C_2-C_6)-alkenyl, (C_1-C_4)-alkoxycarbonyl or tetrahydrofuran-2-ylmethyl,

and

R^{15} represents hydrogen or (C_1-C_4)-alkyl,

or a salt, hydrate, hydrate of the salt or solvate thereof.

3. A compound of the formula (I) according to claim 1,

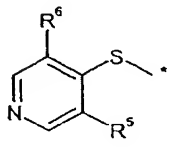
in which

R^1 represents amino,

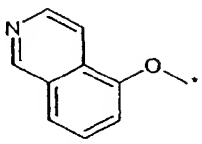
R^2 represents hydrogen,

R^3 and R^4 independently of one another represent hydrogen, fluorine or chlorine,

A represents a radical



or



,

in which

R^5 and R^6 represent hydrogen,

D (1) represents a radical which is selected from the group consisting of

quinoline, indole, pyrazine, pyridazine and triazine, where the rings are in each case attached via a carbon atom,

or

(2) represents a radical *-OR^7

in which

R^7 represents phenyl which may be substituted by fluorine, chlorine, (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy or 1,2-dioxymethylene,

(C_1-C_6)-alkyl or (C_3-C_8)-cycloalkyl which for their part may be substituted by hydroxyl or *-NR^8R^9,

in which

R^8 and R^9 independently of one another represent hydrogen or (C_1-C_4)-alkyl or

R^8 and R^9 together with the nitrogen atom to which they are attached form a morpholine or piperazine ring, where the second nitrogen atom of the piperazine ring may be substituted by (C_1-C_4)-alkyl,

or

(3) represents a radical *-$NR^{10}R^{11}$,

in which

R^{10} represents hydrogen or (C_1-C_4)-alkyl and

R^{11} represents amino-substituted (C_3-C_8)-cycloalkyl or a radical *-$(CH_2)_y$-E,

in which

y represents 0 or 1 and

E represents pyrrolidine or pyridyl, which for their part may be substituted by (C_1-C_4)-alkyl,

or

R^{10} and R^{11} together with the nitrogen atom to which they are attached form a pyrrolidine or piperidine ring which may be substituted by *-$NR^{12}R^{13}$, 1,1-dioxymethylene, (C_1-C_4)-alkoxymethyl or 5- or 6-membered heterocyclyl having one or two heteroatoms N and/or O, which for its part may be substituted by (C_1-C_4)-alkyl,

in which

R^{12} and R^{13} independently of one another represent hydrogen, (C_1-C_6)-alkyl, (C_3-C_8)-cycloalkyl or (C_1-C_4)-alkanoyl or

R^{12} and R^{13} together with the nitrogen atom to which they are attached form a 5- or 6-membered heterocycle,

or

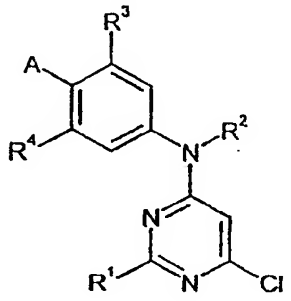
R^{10} and R^{11} together with the nitrogen atom to which they are attached form an 8- to 10-membered bicyclic heterocycle which is fused or spirocyclic and may have one or two further heteroatoms from the group consisting of N and O and which may be substituted by (C_1-C_4)-

alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkanoyl or benzyl,

or a salt, hydrate, hydrate of the salt or solvate thereof.

4. Process for preparing a compound of the formula (I) according to claim 1, wherein either

[A] a compound of the formula (II)



(II),

in which

A, R^1, R^2, R^3 and R^4 are as defined in claim 1,

is reacted with a compound of the formula (III)

$$D\text{-}X^1 \qquad (III)$$

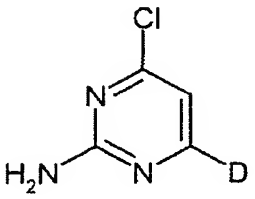
in which

D is as defined in claim 1 and

X^1 represents hydrogen or *-$B(OH)_2$

or

[B] a compound of the formula (IV)

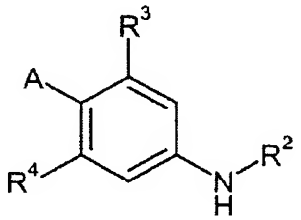


(IV),

in which

D is as defined in claim 1

is reacted with a compound of the formula (V)



(V),

in which

A, R^2, R^3 and R^4 are as defined in claim 1.

5. A compound of the formula (I) as defined in claim 1, 2 or 3, or a salt, hydrate, hydrate of the salt or solvate thereof, for the treatment and/or prophylaxis of a disorder.

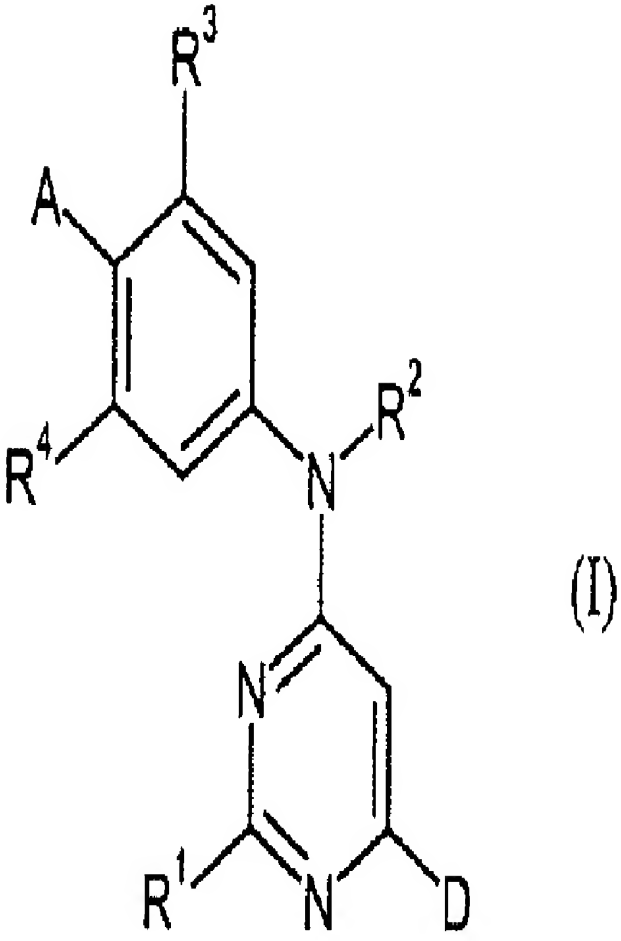
6. Pharmaceutical composition, comprising at least one compound of the formula (I) as defined in claim 1, 2 or 3, or a salt, hydrate, hydrate of the salt or solvate thereof, and at least one auxiliary.

7. Pharmaceutical composition, comprising at least one compound of the formula (I) as defined in claim 1, 2 or 3, or a salt, hydrate, hydrate of the salt or solvate thereof, and at least one further active compound.

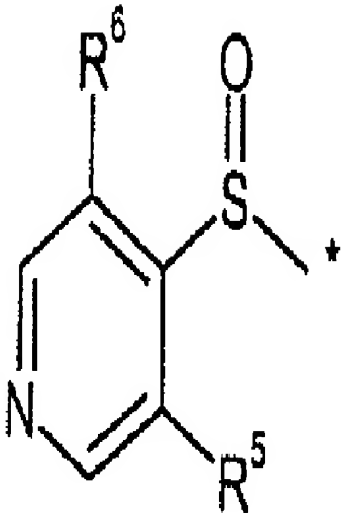
8. Use of a compound of the formula (I) as defined in claim 1, 2 or 3, or a salt, hydrate, hydrate of the salt or solvate thereof, for preparing a pharmaceutical for the treatment and/or prophylaxis of a cardiovascular disorder.

9. Use of a compound of the formula (I) as defined in claim 1, 2 or 3, or a salt, hydrate, hydrate of the salt or solvate thereof, for the treatment and/or prophylaxis of a cardiovascular disorder.

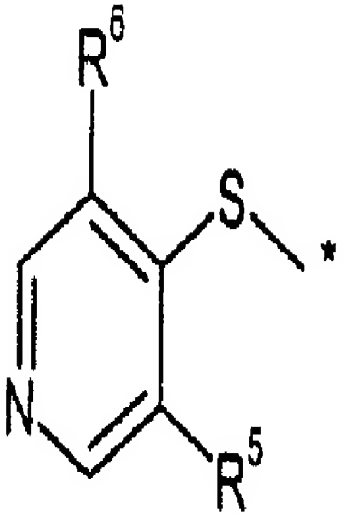
10. The pharmaceutical composition as defined in claim 6 or 7, for the treatment and/or prophylaxis of a cardiovascular disorder.



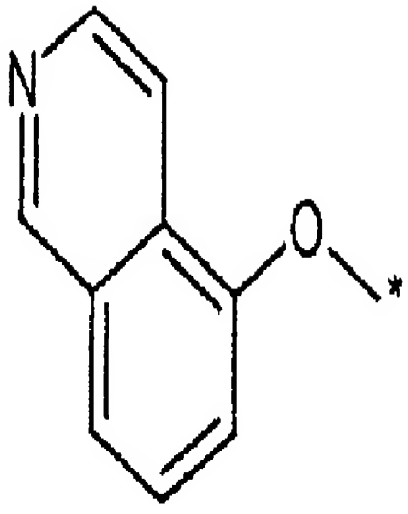
(I)



(II)



(III)



(IV)